CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215446Orig1s000

NON-CLINICAL REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA/BLA REVIEW AND EVALUATION

Application number:	215446
Supporting documents:	1, 7
Applicant's letter date:	November 11, 2021
CDER stamp date:	November 11, 2021
Product:	Edaravone oral suspension
Indication:	Amyotrophic lateral sclerosis
Applicant:	Mitsubishi Tanabe Pharma Development America, Inc.
Clinical Review Division:	DN1
Reviewer:	David L. Carbone, Ph.D.
Supervisor:	Lois M. Freed, Ph.D.
Division Director (DN1):	Teresa Buracchio, M.D.
Project Manager:	Susan Daugherty, R.N.

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1 Executive Summary

1.1 Introduction

RADICAVA ORS (edarvone oral suspension) is an oral formulation of edaravone that has been developed by Mitsubishi Tanabe Pharma Development. Edaravone for IV administration was developed by the same sponsor and was approved on May 5, 2017, for the treatment of ALS.

1.2 Brief Discussion of Nonclinical Findings

The sponsor relied on the same nonclinical package reviewed under NDA 209176 to support development of RADICAVA ORS. However, due to concerns over peripheral neuropathy that was observed in dogs and monkeys following continuous IV infusion (but not IV bolus) with edaravone, the sponsor conducted additional chronic toxicity studies to assess the potential for similar effects following oral administration.

Chronic toxicity studies assessed daily oral administration of edaravone for 26 weeks in male and female Sprague Dawley (SD) rats (0, 25, 75, and 250 mg/kg) and 39 weeks in male and female beagle dogs (0, 10, 30, 100, and 300 mg/kg). The primary toxicities in rat were weight loss and signs of regenerative anemia in HDM and HDF; however, neither of these effects were observed in recovery animals, indicating that both were reversible. In dogs, dosing was suspended between Days 17 and 23 (HD) and Days 44 to 65 (HMD) due to the appearance of clinical signs consistent with neuropathy (i.e., abnormal gait, loss of patellar reflex, and inability to stand). Two HDM (Nos. 10502 and 10503) were euthanized on Day 54 due to unresolved clinical signs and secondary complications (excoriation and purpura on the forelimbs); all other affected animals remained off drug until their symptoms resolved, between Days 105 to 127 (HMD) and Days 99 to 127 (HD), after which they were necropsied. Histopathology findings correlating with the clinical signs included spinal cord white matter vacuolation and vacuolation and atrophy of the sciatic nerve. The NOAEL for oral administration in dogs was 30 mg/kg (C_{max} = 2,521 ng/mL and $AUC_{0\text{-}24h}$ = 3578 ng*h/mL), which provides for an approximate 2-fold safety margin relative to exposure in humans at the recommended dose.

A complete battery of reproductive and developmental toxicity studies was reviewed under NDA 209176. IV doses greater than 3 mg/kg administered from GDs 7 to 17 in rats resulted in decreases in fetal body weight and slight delays in markers of development. IV administration of 100 mg/kg in rabbits increased fetal death. Pre- and postnatal development studies in rats administered 0, 3, 20, or 200 mg/kg edaravone resulted in increased numbers of stillborn offspring at 200 mg/kg, and slight increases in open field activity and rearing behavior in offspring at 20 and 200 mg/kg. Reproductive and developmental toxicity following oral dosing was not assessed.

Edaravone was negative in a complete battery of genetic toxicity assays and was negative in a 26-week carcinogenicity study inTg.rasH2 mice and a 2-year carcinogenicity study in SD rats (*reviewed under NDA 209176).*

1.3 Recommendations

1.3.1 Approvability

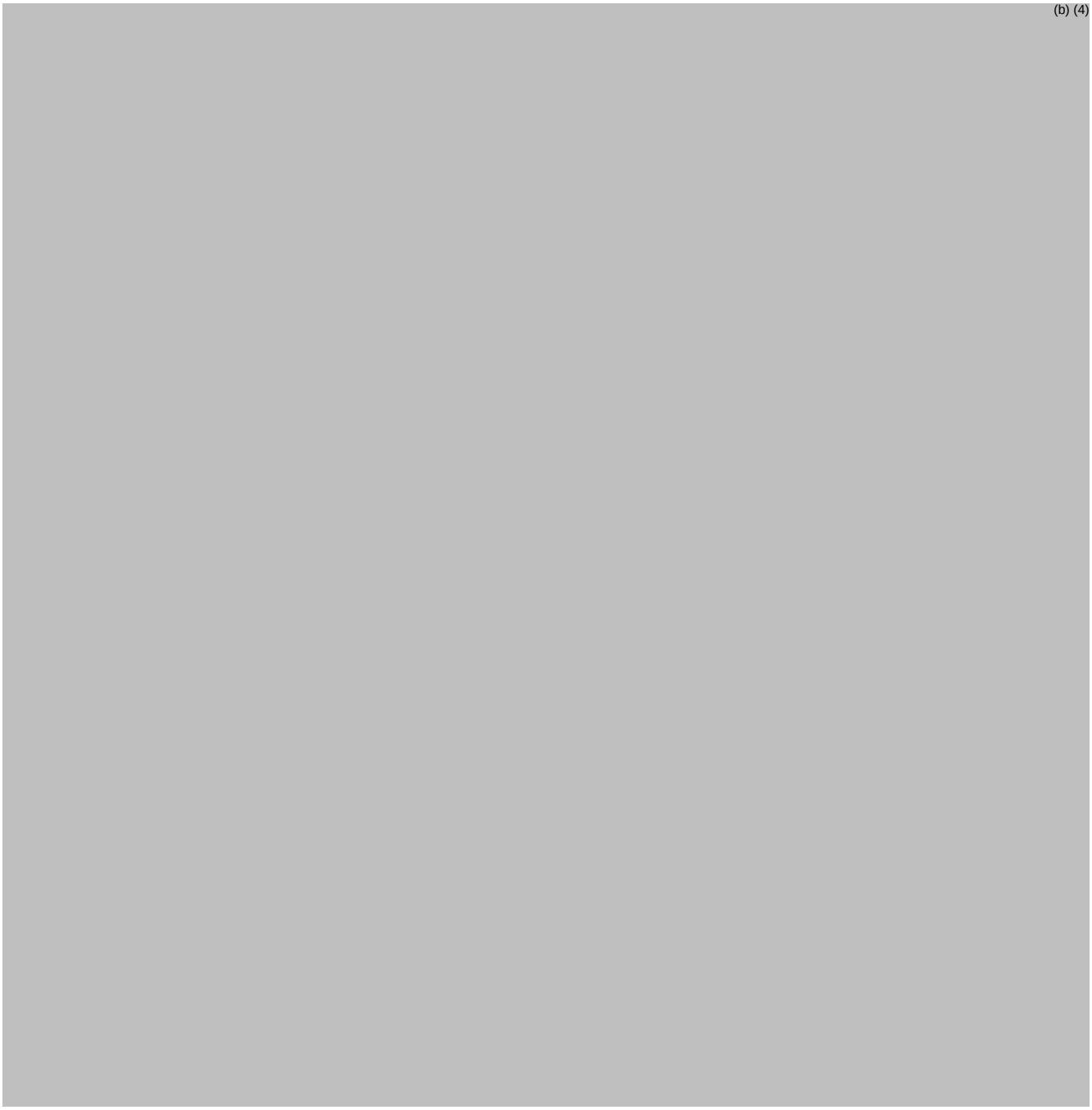
The nonclinical data support approval.

1.3.2 Additional Nonclinical Recommendations

None

1.3.3 Labeling

(b) (4)



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2 Drug Information

2.1 Drug

CAS Registry Number: 89-25-8

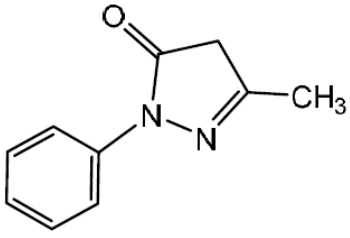
Generic Name: Edaravone ORS

Code Name: MCI-1186

Chemical Name: 5-methyl-2-phenyl-2, 4-dihydro-3H-pyrazol-3-one (IUPAC)

Molecular Formula/Molecular Weight: $H_{10}H_{10}N_2O$, 174.20 g/mol

Structure or Biochemical Description



(Sponsor's Figure)

Pharmacologic Class: Free radical scavenger

2.2 Relevant INDs, NDAs, BLAs and DMFs

Mitsubishi Tanabe Pharma Development:

IND 126396: DN1, Edaravone IV formulation

IND 138145: DN1, Edaravone oral suspension
NDA 209176: DN1, Edaravone IV formulation

2.3 Drug Formulation

RADICAVA ORS is formulated as a suspension, with strengths of 735 and 1050 mg in 35 and 50 mL, respectively.

2.4 Comments on Novel Excipients

RADICAVA ORS is formulated using conventional excipients.

2.5 Comments on Impurities/Degradants of Concern

Based on discussion with the CMC team, there are no concerns regarding impurities or degradants.

2.6 Proposed Clinical Population and Dosing Regimen

RADICAVA ORS is intended to treat ALS. The recommended dose is 105 mg once daily for 14 days followed by a 14-day drug-free period. Subsequent dose is to be 105 mg once daily for 10 days followed by a 14-day drug-free period. Based on discussion with Clinical Pharmacology team, the proposed dosing regimen is intended to result in systemic exposure similar to that resulting from IV administration of RADICAVA (C_{max} = 1500 ng/mL, AUC_{0-t} = 1645 ng*h/mL, AUC_{0-inf} = 1665 ng*h/mL).

2.7 Regulatory Background

preIND WRO: March 9, 2018
IND submission: February 20, 2020
EOP2 meeting minutes: August 14, 2019
PreNDA WRO: September 2, 2021

3 Studies Submitted

3.1 Studies Reviewed

- PK and metabolite profiling following oral dosing in rat and dog (reviewed under IND 126396)
- 2-week repeat oral dosing in SD rat (reviewed under IND 126396)
- 2-week repeat oral dosing in beagle dog
- 26-week repeat oral dosing in rat
- 39-week repeat oral dosing in beagle dog (reviewed under IND 138146)

<u>Studies reviewed under NDA 209176:</u>
In vitro and *in vivo* primary pharmacology.
Secondary pharmacology.
Safety pharmacology.
PK/ADME in mice rats, dogs, and monkeys.
Single dose toxicology in mice (oral, SC, IV), rats (oral, SC, IV), and dogs (IV).
Repeat IV dose toxicology in rats, dogs, and monkeys.

Fertility and early embryonic development in rats.
Embryofetal development in rats and rabbits.
Pre- and postnatal development in rats.
Juvenile animal toxicology in rats and dogs.
In vitro (Ames, mammalian chromosomal aberration) and *in vivo* (mouse micronucleus) genotoxicity assays.
Mechanistic studies for neurodegeneration (dogs) and renal toxicity (rats).
Local and vascular irritation in rabbits.
Studies to assess hemolysis, antigenicity, dependence, metabolite toxicity and impurities.
26-week carcinogenicity study in Tg.rasH2. 2-year carcinogenicity study in SD rat.

3.2 Studies Not Reviewed

Primary pharmacology studies in models of stroke.

3.3 Previous Reviews Referenced

NDA 209176:

- Nonclinical review by David Carbone (NDA; March 27, 2017)
- Nonclinical review by David Carbone (26-week carcinogenicity study in Tg.rasH2 mice; August 6, 2021)
- Nonclinical review by David Carbone (2-year carcinogenicity study in SD rat; April 6, 2022)

IND 126396:

- Nonclinical review by David Carbone (PK and metabolite profiling following oral dosing in rat and dog, 2-week repeat oral dosing in SD rat; October 4, 2019)

IND 138145:

- Nonclinical review by David Carbone (39-week study in beagle dog; July 5, 2019)

4 Pharmacology

4.1 Primary Pharmacology

(From nonclinical review of NDA 209176)
MCI-186 (edaravone) is thought to reduce cell injury through scavenging oxygen radicals. *In vitro* studies demonstrated prevention of linoleic acid oxidation by hydrogen peroxide and ferrous ions, reductions in lipid peroxidation in rat brain homogenate and isolated mitochondria, reduced oxidative injury to cultured endothelial cells, and reduced neuronal apoptosis in a model of excitotoxicity. However, IV administration of 3 or 6 mg/kg MCI-186 did not reduce neuronal cell death in a rat model of nerve avulsion. In a SOD-mutant transgenic rat model of ALS, a life-long regimen consisting of once-daily IV injection of 3 mg/kg MCI-186 for 2 days followed by a 2-day drug holiday did not increase lifespan or generally improve performance in a battery of reflex or strength tests, although a slight improvement was observed in the incline plane test.

4.2 Secondary Pharmacology

(From nonclinical review of NDA 209176)
There were no significant interactions between MCI-186 or its sulfate or glucuronide conjugates in an *in vitro* panel of 79 receptors, ion channels, and transporters.

4.3 Safety Pharmacology

(From nonclinical review of NDA 209176):
In safety pharmacology studies, *in vitro* concentrations of up to 1 mM edaravone did not inhibit the hERG current. CNS signs generally included increases in lacrimation and ptosis, and decreases in spontaneous movement in male mice and rats following a single IV dose of 30 or 100 mg/kg edaravone. Decreases in body temperature were observed in male mice administered a single 100 mg/kg IV injection of edaravone. In mongrel dogs, single IV administration of 30 or 100 mg/kg edaravone resulted in transient decreases in blood pressure and increases in carotid blood flow and heart rate. Single IV injection of up to 100 mg/kg edaravone in mongrel dogs did not affect respiratory rate; however, neither tidal or minute volumes nor hemoglobin oxygen saturation were evaluated.

5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME

Standard PK parameters were assessed following oral administration of edaravone in mouse, dog and rat. Additionally, metabolite profiling studies were conducted following oral dosing in rat and dog, indicating the formation of sulfate and glucuronide conjugates. TK parameters following IV or SC dosing in mouse, rat, and dog were reviewed under NDA 209176.

Route	Species	Dose (mg/kg)	C_{max} (ng/mL)	T_{max} (h)	AUC (ng×h/mL)	$t_{1/2}$ (h)	F (%)
Oral	Mouse	10	357.23	0.25	248.58	1.45	N/A
		30	1135.08	0.25	532.68	1.55	N/A
		100	12737.67	0.25	4925.45	1.51	N/A
	Rat	10	243.38	0.25	225.63	0.77	8.11
		30	1313.50	0.25	1097.59	2.46	13.85
		100	10998.68	0.25	8018.44	1.57	29.94
	Dog	5	132.52	0.25	84.08	1.26	16.9
		10	686.08	0.25	399.87	1.83	18.7
		30	9557.82	0.33	4946.17	2.59	75.8

6 General Toxicology

(Toxicity studies following IV or SC dosing were reviewed under NDA 209176)

6.1 Single-Dose Toxicity

Summarized from nonclinical review for NDA 209176:
Single oral doses greater than 1300 mg/kg in mouse and 1560 mg/kg in rat resulted in mortality due to respiratory or acute cardiac failure.

6.2 Repeat-Dose Toxicity

Rat (*summarized from nonclinical review for IND 126396*):
Daily oral administration of 0, 30, 100, 300, and 1000 mg/kg edaravone for 2 weeks was evaluated in male and female SD rats (10/sex/group). In males, dose-dependent reductions in body weight gain relative to controls of 8, 8, 12, and 35%, respectively, were observed. In females, a reduction in body weight gain (30%) relative to controls was only observed at the high dose. Additional drug-related toxicity consisted of regenerative anemia in HDM and HDF.

Dog
Male and female beagle dogs (3/sex/group) were administered 0, 10, 30, 100, and 300 mg/kg edaravone by daily oral gavage for 2 weeks. All animals survived and there were no drug-related clinical signs, including effects on patellar reflex. Adverse hematology findings consisted of signs of regenerative anemia in HDM, MDF, and HDF. Histopathology findings consisted of extramedullary hematopoiesis in the spleen. Recovery was not assessed.

Study title: A 26-week oral repeated dose toxicity study of edaravone in rats followed by a 5-week recovery period

Study no.:	B180034
Study report location:	EDR
Conducting laboratory and location:	(b) (4)
Date of study initiation:	February 6, 2018
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	Edaravone, Lot U032ED, 100.1%

Methods

Doses:	0, 25, 75, 250 mg/kg (main) 0, 250 mg/kg (recovery)
Frequency of dosing:	Daily
Route of administration:	Oral gavage
Dose volume:	10 mL/kg
Formulation/Vehicle:	(b) (4) gum aqueous solution
Species/Strain:	SD
Number/Sex/Group:	12 (main), 6 (recovery)
Age:	6 weeks at initiation of dosing
Weight:	165.5 g to 211.8 g (males) 150.2 to 194.6 g (females)
Satellite groups:	TK arm
Unique study design:	No unique elements
Deviation from study protocol:	No significant deviations

Observations and Results

Mortality and Clinical Signs

All animals were monitored three times daily for mortality or signs of morbidity. There was no drug-related mortality. Drug related clinical signs consisted of salivation in males and females at doses greater than 25 mg/kg.

Body Weights and Food Consumption

Body weight and food consumption were assessed weekly. Significant decreases in body weight were observed in HDM and HDF and were accompanied by slight decreases in food consumption.

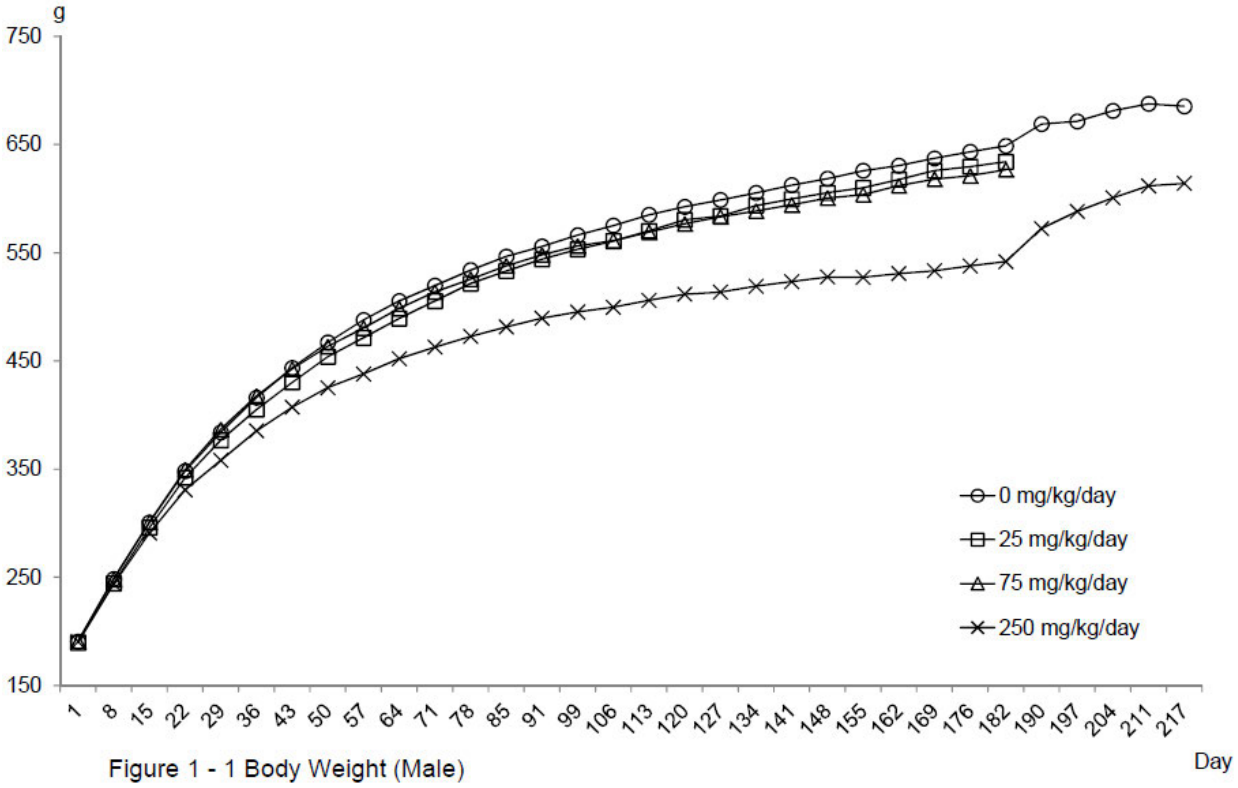


Figure 1 - 1 Body Weight (Male)

(Sponsor's Figure)

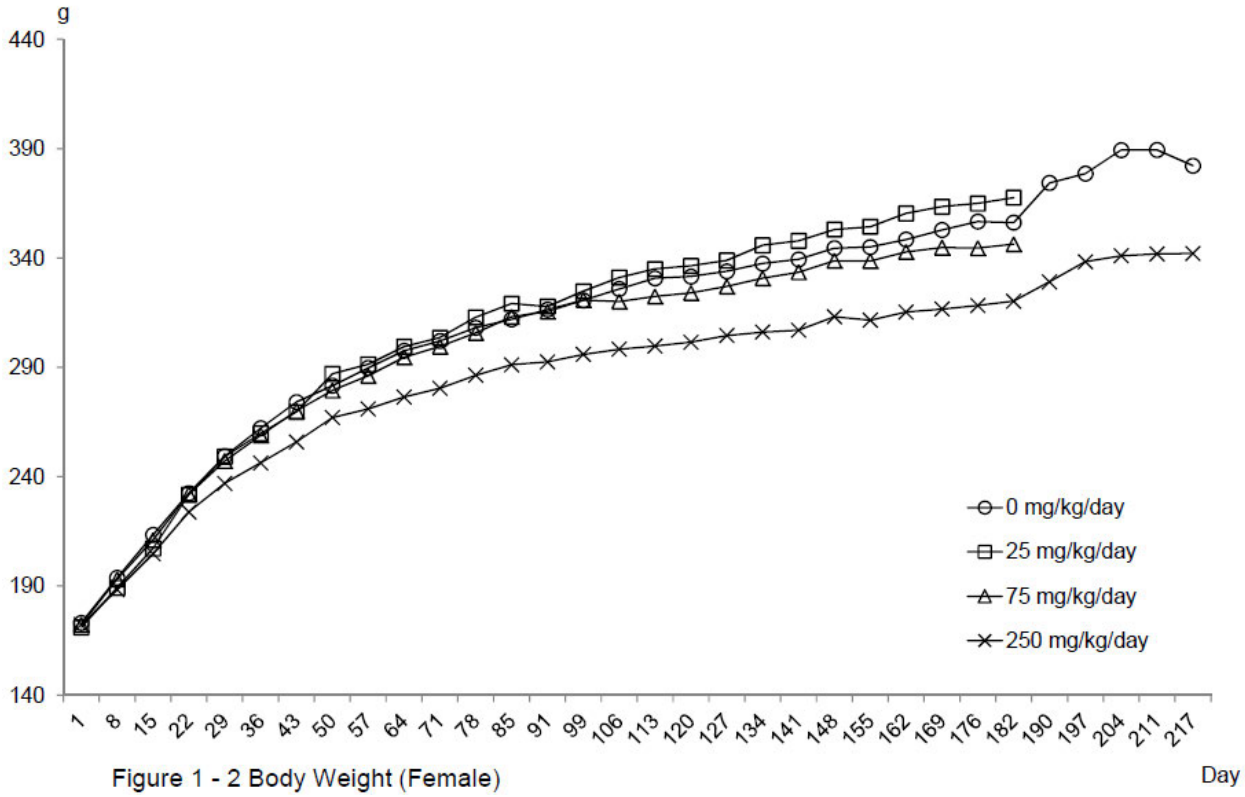


Figure 1 - 2 Body Weight (Female)

(Sponsor's Figure)

Ophthalmoscopy

Direct and indirect ophthalmoscopy and slit lamp biomicroscopy were conducted prior to the initiation of dosing and during Weeks 26 (main), and 31 (recovery). There were no drug-related findings.

ECG

Not evaluated

Hematology, Clinical Chemistry, and Urinalysis

Blood samples for hematology and clinical chemistry were collected from fasted animals at the time of necropsy. Urinalysis parameters were assessed during Weeks 26 and 31. There were no drug effects on clinical chemistry parameters. Hematology parameters indicated signs of regenerative anemia. Urinalysis indicated the presence of occult blood and RBCs in 2 HDM. Similar hematology and urinalysis findings were not present in recovery groups.

Finding	Sex	Main (mg/kg)				Recovery (mg/kg)	
		0	25	75	250	0	250
Hematology							
RBC (10^6/µL)	M	8.613	8.353	8.452	7.912	8.097	8.333
	F	7.498	7.251	7.616	6.772	7.513	7.290
Hb (g/dL)	M	15.58	15.03	15.33	14.99	14.58	15.18
	F	14.74	14.27	14.72	13.68	14.23	14.33
Hct (%)	M	40.87	39.33	40.19	40.15	39.42	40.68
	F	38.88	37.44	38.58	36.57	37.77	37.97
MCV (fL)	M	47.52	47.11	47.59	50.80	48.68	48.80
	F	51.88	51.72	50.66	54.03	50.30	52.10
MCH (pg)	M	18.11	18.02	18.13	18.97	18.03	18.22
	F	19.66	19.71	19.33	20.19	18.95	19.67
MCHC (g/dL)	M	38.12	38.24	38.13	37.33	36.98	37.32
	F	37.93	38.11	38.14	37.39	37.68	37.75
Retic (10^9/µL)	M	224.93	237.06	231.09	297.08	276.05	216.23
	F	187.44	180.21	197.92	254.29	171.02	159.87
Urinalysis							
Occult Blood	M	0/6	0/6	0/6	2/6	0/6	0/6
	F	0/6	0/6	0/6	0/6	0/6	0/6
RBC	M	0/6	0/6	0/6	2/6	0/6	0/6
	F	0/6	0/6	0/6	0/6	0/6	0/6

Gross Pathology and Organ Weights

There were no drug-related gross findings or effects on organ weights.

Histopathology

Adequate Battery: Yes

Heart	Ileum	Vagina
Aorta	Cecum	Pituitary gland
Mandibular LN	Colon	Thyroid/parathyroid
Mesenteric LN	Rectum	Adrenal gland
Thymus	Salivary glands	Brain
Spleen	Liver	Cervical SC
Femur (bone and marrow)	Pancreas	Thoracic SC
Sternum (bone and marrow)	Kidney	Lumbar SC
Trachea	Urinary bladder	Eye/optic nerve
Lungs/bronchus	Testis	Harderian gland
Tongue	Epididymides	Skeletal muscle
Esophagus	Seminal Vesicle	Sciatic nerve
Stomach	Prostate	Skin
Duodenum	Ovary	Mammary gland
Jejunum	Uterus	Lesions

Signed Pathology Report: Yes

Peer Review: Yes

Histological Findings: Histology findings considered to be drug-related consisted of extramedullary hematopoiesis in the spleen and acinar cell hypertrophy in the submandibular gland in HDM and HDF, and renal papillary necrosis in 1/12 HDM. There were no drug-related findings in the recovery groups.

Organ Findings	Status:	At the end of the dosing period								At the end of the recovery period			
	Sex:	Male				Female				Male		Female	
	Dose level (mg/kg/day):	0	25	75	250	0	25	75	250	0	250	0	250
	Number of animals examined:	12	12	12	12	12	12	12	12	6	6	6	6
	(Grade)												
Spleen													
Increase, extramedullary hematopoiesis, erythrocytic	1	0	0	0	1	0	0	0	2	0	0	0	0
Submandibular gland													
Hypertrophy, acinar cell	1	0	0	0	1	0	0	0	2	0	0	0	0
Kidney													
Necrosis, papilla	1	0	0	0	1	0	–	–	0	0	0	–	–

Grade: 1, minimal
–, Not examined
Data are shown as the number of animals affected.

(Sponsor's Table)

Special Evaluation

Not evaluated.

Toxicokinetics

TK parameters were evaluated on Days 1 and 182 for edaravone and its glucuronide and sulfate conjugates.

Parameter	Day	Males (mg/kg			Females (mg/kg)		
		25	75	250	25	75	250
Edaravone							
C_{max} (ng/mL	1	621.5	8685	23060	1722	12580	35230
	182	4141	15620	45700	3475	19740	70590
AUC_{0-24h} (ng*h/mL)	1	571	4293	22600	1136	6793	29810
	182	2241	10670	71600	2223	12590	119200
t_{max} (h)	1	0.3	0.3	0.3	0.3	0.3	0.3
	182	0.3	0.3	0.3	0.3	0.3	0.3
2212119 (Sulfate Conjugate)							
C_{max} (ng/mL	1	26320	40280	61200	32060	40850	66590
	182	35530	48810	70870	53210	70870	86160
AUC_{0-24h} (ng*h/mL)	1	23320	65540	299000	25080	68880	312300
	182	34010	120500	292500	45780	166500	431600
t_{max} (h)	1	0.3	0.3	0.4	0.3	0.3	0.4
	182	0.3	0.3	0.4	0.3	0.5	0.5
2218429 (Glucuronide Conjugate)							
C_{max} (ng/mL	1	9053	28480	37600	8908	22770	52950
	182	16770	24190	39460	9924	25090	76970
AUC_{0-24h} (ng*h/mL)	1	7166	24370	101500	6113	20510	106800
	182	11600	36450	184400	8054	33940	217300
t_{max} (h)	1	0.3	0.3	0.3	0.3	0.3	0.4
	182	0.3	0.4	0.6	0.3	0.3	0.8

Dosing Solution Analysis

Dosing solutions ranged from 97.6 to 101.6% of their intended target concentrations.

From Nonclinical Review of IND 138145:

Study title: A 39-week oral repeated dose toxicity study of edaravone in dogs followed by a 5-week recovery period

Study no.:	B171033
Study report location:	EDR
Conducting laboratory and location:	(b) (4)
Date of study initiation:	39
GLP compliance:	weeks
QA statement:	Y
Drug, lot #, and % purity:	Edaravone, Lot U032ED, 100.1%

Methods

Doses:	0, 10, 30, 100, 300 mg/kg (main) 0, 300 mg/kg (recovery)
Frequency of dosing:	Daily
Route of administration:	4 main; 2 recovery (C and HD)
Dose volume:	5 mL/kg
Formulation/Vehicle:	(b) (4) gum aqueous solution
Species/Strain:	Beagle Dog
Number/Sex/Group:	4 (main), 2 (recovery)
Age:	6 to 7 months at initiation of dosing
Weight:	6.8 to 9.1 kg (males) 6.4 to 8.5 kg (females)
Satellite groups:	None
Unique study design:	None
Deviation from study protocol:	Dosing was suspended in all MHD and HD animals due to neurotoxicity. Necropsies were conducted in all surviving MHD and HD animals after clinical signs of neurotoxicity resolved.

Observations and Results

Mortality and Clinical Signs

Animals were monitored 4 times daily for mortality or signs of morbidity. Clinical signs consisting of abnormal gait, loss of patella reflex, and/or an inability to stand were observed at 100 and 300 mg/kg, resulting in discontinuation of dosing in all MHD and HD animals between Days 17 to 23 (HD) and 44 to 65 (HMD). Two HDM (Nos. 10502 and 10503) were euthanized on Day 54 due to unresolved clinical signs and secondary complications (excoriation and purpura on the forelimbs); all other animals in the MHD and HD groups were remained off drug until their symptoms resolved, after which they were necropsied. There were no drug-related clinical signs at 10 or 30 mg/kg.

Dose level (mg/kg/day)	Sex	Animal number	Day of discontinuation of administration	Day of recovery from all findings	Day of sacrifice
100	Male	10401	Day 58	Day 92	Day 105
		10402	Day 44	Day 86	Day 105
		10403	Day 58	Day 106	Day 127
		10404	Day 58	Day 99	Day 105
	Female	50401	Day 58	Day 106	Day 121
		50402	Day 51	Day 99	Day 121
		50403	Day 58	Day 106	Day 121
		50404	Day 65	Day 106	Day 121
		50501	Day 58	Day 106	Day 121
		50502	Day 65	Day 99	Day 121
300	Male	10502	Day 23	-	-
		10503	Day 23	-	-
		10504	Day 30	Day 86	Day 105
		10505	Day 21	Day 117	Day 127
		10506	Day 23	Day 86	Day 105
	Female	50503	Day 22	Day 86	Day 99
		50504	Day 17	Day 86	Day 99
		50505	Day 22	Day 101	Day 121
		50506	Day 20	Day 78	Day 99

-: Not applicable

*6: Euthanized for humane reasons on Day 54.

(Sponsor's Table)

Body Weights and Food Consumption

Animals were weighed weekly, and food consumption was evaluated daily. There were no drug effects on body weight or food consumption.

Ophthalmoscopy

Slit lamp and indirect ophthalmoscopy were conducted prior to dosing and during Weeks 13, 26, and 39; there were no drug-related effects.

ECG

ECG was evaluated prior to the initiation of dosing and during Weeks 12, 13, 25, and 38. There were no drug effects on ECG parameters.

Hematology, Clinical Chemistry, and Urinalysis

Blood samples were collected prior to the initiation of dosing, during Weeks 13, 26, and 39, and prior to necropsy. Urine samples were collected from fasted animals prior to the initiation of dosing and during Weeks 12 or 13, 25 or 26, and 38 or 39. There were no drug-related effects on hematology, clinical chemistry, or urinalysis parameters.

Gross Pathology and Organ Weights

There were no drug-related gross findings or effects on organ weights

Histopathology

Adequate Battery: Yes

Heart	Jejunum	Vagina
Aorta	Ileum	Pituitary Gland
Thoracic LN	Cecum	Thyroid Gland
Mandibular LN	Colon	Parathyroid Gland
Mesenteric LN	Rectum	Adrenal Gland
Thymus	Salivary Glands	Brain
Spleen	Liver	Cervical SC
Bone (femur and sternum)	Gallbladder	Thoracic SC
Bone Marrow (femur and sternum)	Pancreas	Lumbar SC
Trachea	Kidney	Eye and Optic Nerve
Lungs	Urinary Bladder	Skeletal Muscle
Tongue	Testis	Sciatic Nerve
Tonsil	Epididymides	Skin
Esophagus	Prostate	Mammary gland
Stomach	Ovary	Macroscopic Lesions
Duodenum	Uterus	

Signed Pathology Report: Yes

Peer Review: Yes

Histological Findings:

There were no drug-related findings at the LD or LMD. For HMD and HD groups, histology evaluations were conducted at unscheduled necropsy (2 HDM; Day 54) and following recovery of clinical signs (i.e., gait abnormalities, loss of patella reflex, and/or inability to rise) in surviving MHD and HD animals (Days 99-127). Drug-related findings included white matter vacuolation in the spinal cord, vacuolation and atrophy of the sciatic nerve, femoral muscle atrophy, and hypospermatogenesis.

Organ	Sex:	Male
Findings	Dose level (mg/kg/day):	300
	Number of animals examined:	2
	(Grade)	
Spinal cord		
Vacuolation, white matter, dorsal funicle	1	2
Sciatic nerve		
Vacuolation	3	2
Atrophy, nerve fiber	1	2
Femoral muscle		
Atrophy, muscle fiber	2	2

(Sponsor's Table; Unscheduled necropsy)

Organ	Sex:	Male		Female	
Findings	Dose level (mg/kg/day):	100	300	100	300
	Number of animals examined:	4	3	6	4
	(Grade)				
Spinal cord					
Vacuolation, white matter, dorsal funicle	1	1	2	1	3
Sciatic nerve					
Vacuolation	1	4	3	6	4
Atrophy, nerve fiber	1	1	2	5	4
Testis					
Hypospermatogenesis	1	2	1	NA	NA
	2	0	1		

Grade: 1, minimal; 2, mild

NA: Not applicable.

Data are shown as the number of animals affected.

(Sponsor's Table; After resolution of clinical signs)

Special Evaluation

None

Toxicokinetics

TK were evaluated for edaravone and the major metabolites, 2212119 (sulfate conjugate) and 2218429 (non-acyl glucuronide conjugate). Increases in C_{max} and AUC

were greater than dose proportional. C_{max} was generally higher in males than in females at 10 and 30 mg/kg. There were no sex differences in TK parameters at higher doses.

Dose (mg/kg/day)	Period (Day)	Sex	N	C_{max} (ng/mL)	t_{max} (h)	AUC_{0-24h} (ng·h/mL)
10	1	Male	4	377.9 ± 184.6	0.3 ± 0.0	524.9 ± 46.0
		Female	4	314.7 ± 169.4	0.3 ± 0.1	504.7 ± 122.7
	22	Male	4	323.4 ± 145.7	0.3 ± 0.1	672.1 ± 80.8
	20	Female	4	248.8 ± 66.7	0.3 ± 0.1	661.6 ± 73.0
	91	Male	4	449.1 ± 325.9	0.3 ± 0.1	661.7 ± 191.9
		Female	4	317.7 ± 54.5	0.3 ± 0.0	616.7 ± 112.2
	182	Male	4	374.7 ± 171.7	0.4 ± 0.4	714.4 ± 54.8
		Female	4	291.5 ± 122.0	0.4 ± 0.1	803.1 ± 158.9
	273	Male	4	508.8 ± 100.0	0.3 ± 0.0	626.0 ± 29.6
		Female	4	311.0 ± 31.3	0.3 ± 0.0	617.7 ± 114.5
30	1	Male	4	4133 ± 2606	0.3 ± 0.0	2745 ± 1025
		Female	4	4496 ± 2773	0.3 ± 0.0	2933 ± 1079
	22	Male	4	4015 ± 845	0.3 ± 0.0	2941 ± 370
	20	Female	4	2700 ± 521	0.3 ± 0.1	2662 ± 345
	91	Male	4	4736 ± 747	0.3 ± 0.0	3348 ± 409
		Female	4	3120 ± 2021	0.3 ± 0.1	2946 ± 580
	182	Male	4	4254 ± 2476	0.3 ± 0.1	3695 ± 735
		Female	4	3562 ± 1921	0.3 ± 0.0	3392 ± 578
	273	Male	4	3722 ± 1874	0.3 ± 0.1	3578 ± 449
		Female	4	2521 ± 1461	0.6 ± 0.3	3719 ± 948
100	1	Male	4	16750 ± 4230	0.5 ± 0.0	20290 ± 3850
		Female	4	34140 ± 11490	0.4 ± 0.1	31800 ± 5030
	22	Male	4	15590 ± 8440	0.4 ± 0.1	16760 ± 8430
	20	Female	4	18560 ± 9950	0.6 ± 0.3	21210 ± 6890
	91	Male*	1	21820 (NC)	0.25 (NC)	17270 (NC)
	182	Male*	1	26980 (NC)	0.5 (NC)	25880 (NC)
	273	Male*	1	36770 (NC)	0.25 (NC)	31450 (NC)
300	1	Male	6	92140 ± 13120	0.8 ± 0.3	160600 ± 22800
		Female	6	105300 ± 42300	0.8 ± 0.3	175100 ± 49900
	22	Male	5	62050 ± 18530	0.7 ± 0.3	110500 ± 31900
	20	Female	2	80840 (NC)	0.8 (NC)	117700 (NC)

*: Administered at 300 mg/kg/day until Day 22 and at 100 mg/kg/day from Day 30
N: Number of animals
NC: Not calculated
Data are shown as the mean ± SD.

(Sponsor's Table; TK for edaravone)

Dosing Solution Analysis

Dosing solutions were within 10% of nominal.

7 Genetic Toxicology

(Reviewed under NDA 209176)
Edaravone was negative in Ames, *in vitro* chromosomal aberration, and mouse *in vivo* micronucleus assays.

8 Carcinogenicity

(Reviewed under NDA 209176)
Edaravone was negative for carcinogenicity in a 26-week study in Tg.rasH2 mice and a 2-year study in SD rats.

9 Reproductive and Developmental Toxicology

(From nonclinical review of NDA 209176):
No effects on fertility were seen in rats administered 0, 3, 20, or 200 mg/kg edaravone by IV injection. No malformations at IV doses up to 300 or 100 mg/kg were observed in rat or rabbit embryofetal development studies, respectively. However, IV doses greater than 3 mg/kg administered from GD 7 to 17 in rats resulted in decreases in fetal body weight and slight delays in markers of development. IV administration of 100 mg/kg in rabbits increased fetal death. Pre- and postnatal development studies in rats administered 0, 3, 20, or 200 mg/kg edaravone resulted in increased numbers of stillborn offspring at 200 mg/kg, and slight increases in open field activity and rearing behavior in offspring at 20 and 200 mg/kg.

10 Special Toxicology Studies

None

11 Integrated Summary and Safety Evaluation

RADICAVA ORS is an oral formulation of edaravone that has been developed by Mitsubishi Tanabe Pharma Development for the treatment of ALS. The IV-administered formulation for edaravone was approved for ALS on May 5, 2017, (NDA 209176). Based on discussion with the Clinical Pharmacology team, the dosing regimens for oral and IV formulations result in similar systemic exposure (C_{max} = 1500 ng/mL, $AUC_{0\text{-}t}$ = 1645 ng*h/mL, $AUC_{0\text{-}inf}$ = 1665 ng*h/mL).

The sponsor generally relied upon the nonclinical studies used to support development of the IV formulation, which were reviewed under NDA 209176. However, although IV bolus administration in the nonclinical studies was generally well-tolerated, 24-hr continuous IV infusion of edaravone in beagle dogs and cynomolgus monkeys resulted in a severe peripheral neuropathy characterized by progressive loss of limb use and degeneration of muscle nerve fibers, sciatic nerve, and cervical and lumbar spinal cord. Based on concern that oral administration of edaravone may result in similar toxicity,

additional chronic toxicity studies were conducted in rat and dog administered daily oral doses of edarvone.

Chronic oral toxicity studies consisted of a 26-week study in male and female SD rats and a 39-week study in male and female beagle dogs. In rats, daily oral doses of 0, 25, 75, and 250 mg/kg edaravone resulted in a significant decrease in body weight gain and signs of regenerative anemia in HDM and HDF. However, neither finding was observed at the end of the recovery period. In dogs, doses of 0, 10, 30, 100, and 300 mg/kg resulted in clinical signs similar to those observed with continuous IV infusion (i.e., abnormal gait, loss of patellar reflex, and inability to stand) at doses above 30 mg/kg. At necropsy, correlating histopathology findings consisted of spinal cord white matter vacuolation and degeneration, and atrophy of the sciatic nerve. Based on these findings, the NOAEL for oral administration of edaravone in dogs was 30 mg/kg, which resulted in C_{max} and $AUC_{0\text{-}24h}$ of 2521 ng/mL and 3578 ng*h/mL, respectively.

Additional safety concerns from the nonclinical studies included decreases in fertility, slight delays in developmental endpoints, and increases in fetal death and stillborn birth following IV bolus administration in a battery of reproductive and developmental studies in rat and rabbit. Because such findings are already reflected in approved labeling for edaravone, no additional reproductive or developmental studies were needed to support the development of RADICAVA ORS with the currently proposed dosing regimen. However, because the peripheral neuropathy observed following continuous IV or oral administration in adult dog and continuous IV infusion in adult monkey was not seen in rat, the potential for neurodevelopmental toxicity following oral administration of edaravone should be further assessed with an enhanced pre and postnatal development study in monkey should the sponsor propose a daily oral dosing regimen for humans.

Although the potential for carcinogenicity was not assessed prior to approval of the IV edaravone formulation, 26-week and 2-year carcinogenicity studies in Tg.rasH2 mice and SD rats, respectively, were completed as postmarketing requirements and indicated that edaravone is negative for carcinogenicity (reviewed under NDA 209176).

The primary toxicity observed with oral administration of edaravone was peripheral neuropathy in dogs for which the NOAEL was 30 mg/kg and resulted in an approximate 2-fold safety margin based on exposure at the recommended human dose for RADICAVA ORS. Based on discussion with the clinical team, the safety margin for peripheral neuropathy is acceptable but the finding should be adequately described in Section 13.2 of the product label. The nonclinical data, therefore, support approval of RADICAVA ORS. However, the finding of peripheral neuropathy in dogs and monkeys administered edaravone by continuous IV infusion and in dogs administered edaravone by oral gavage raise additional concerns regarding the potential for developmental toxicity given that such findings were not present in rats following IV bolus, continuous infusion, or

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/s/

DAVID L CARBONE
05/11/2022 02:03:16 PM

LOIS M FREED
05/11/2022 02:23:09 PM
I concur.