CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215446Orig1s000

CLINICAL REVIEW(S)

CLINICAL REVIEW

Application Type	505(b)(1)
Application Number(s)	NDA 215446
Priority or Standard	Standard
Submit Date(s)	November 12, 2021
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Division/Office	Office of Neuroscience/Division of Neuroscience 1 (DN1)
Reviewer Name(s)	John S. Troiani, MD, PhD
Review Completion Date	05/06/2022
Established/Proper Name	Edaravone (oral)
(Proposed) Trade Name	RADICAVA ORS
Applicant	Mitsubishi Tanabe Pharma Corporation
Dosage Form(s)	Oral suspension
Applicant Proposed Dosing Regimen(s)	105 mg (5 mL) orally or by feeding tube once daily in cyclic fashion: - Initial treatment cycle: daily dosing for 14 days followed by a 14-day drug-free period - Subsequent treatment cycles: daily dosing for 10 days out of 14-day periods, followed by 14-day drug-free periods
Applicant Proposed Indication(s)/Population(s)	Treatment of amyotrophic lateral sclerosis (ALS)
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Treatment of ALS

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Glossary

AC	advisory committee
ADL	activities of daily living
AE	adverse event (in this review, AE is used for TEAE (below))
Afib	atrial fibrillation
ALS	amyotrophic lateral sclerosis
A01	Study MT-1186-A01
AR	adverse reaction
BA	bioavailability
BE	bioequivalence
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
C-SSRS	Columbia-Suicide Severity Rating Scale
DMC	data monitoring committee
ECG	electrocardiogram (12-lead)
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
FVC	Forced Vital Capacity
%FVC	Percent of predicted FVC
GCP	good clinical practice
GI	gastrointestinal
GRMP	good review management practice

ICH	International Council for Harmonization
IND	Investigational New Drug Application
IR	information request
IV or I.V.	intravenous
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
J03	Study MT-1186-J03
MCI-186	IV edaravone
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
MT-1186	oral edaravone
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information or package insert
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PN	peripheral neuropathy
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
PT	preferred term (MedDRA)
REMS	risk evaluation and mitigation strategy
RRA	remote regulatory assessment
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	system organ class (MedDRA)
TE	treatment emergent (after at least 1 dose of study medication was taken)
TEAE	treatment emergent adverse event (
TESAE	treatment emergent serious adverse event

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1. Executive Summary

1.1. Product Introduction

RADICAVA (edaravone) is an intravenously infused, free-radical scavenger molecule approved by the FDA in 2017 (NDA 209176) for the treatment ALS. RADICAVA is administered as an intravenous infusion of 60 mg over 60 minutes in monthly cycles, as follows. The loading dose is infused once daily for 14 days, followed by a 14-day drug-free period, then followed by repeat maintenance cycles consisting of a once daily dose for 10 days (out of a 14-day block) then a 14-day drug-free block (e.g., 10 days ON then 18 days OFF).

The potential for convenience and better compliance with dosing recommendations led to the development of RADICAVA ORS. RADICAVA ORS suspension is taken as an oral or G-tube (NGT or PEG) dose of 105 mg (5 mL). The 105 mg dose was determined to be bioequivalent to a 60 mg IV dose infused over 60 minutes in bioavailability (BA) Study MT-1186-J03.

This application is a 505 (b)(1) application based on a bioequivalence study to bridge the safety and efficacy of the proposed 105 mg RADICAVA oral formulation to the approved 60 mg RADICAVA intravenous formulation infused over 60 minutes.

1.2. Conclusions on the Substantial Evidence of Effectiveness

This is a 505 (b)(1) application based on a pivotal bioequivalence study (J01) to bridge the efficacy of the new oral RADICAVA ORS formulation to the approved intravenous RADICAVA formulation. The Office of Clinical Pharmacology team reviewed the results of the pivotal bioequivalence study (MT-1186-J03), and concluded RADICAVA ORS 105 mg oral suspension formulation is bioequivalent for AUC to the reference RADICAVA 60 mg intravenous formulation (see Clinical Pharmacology Review). However, Cmax was higher for the oral formulation than the IV, so additional long-term safety was required.

1.3. Benefit-Risk Assessment

The oral formulation overcomes the difficulties associated with repeated intravenous administration, such as the need for trained personnel, difficult I.V. access, pain, bleeding, bruising, infection, and inconvenience, among others. The safety profile of the new oral formulation is comparable to the approved RADICAVA intravenous formulation, and efficacy has been demonstrated by bioequivalence.

2. Therapeutic Context

2.1. Analysis of Condition

ALS is a rare (2 in 100,000 individuals per year), fatal neurodegenerative disease that affects both upper and lower motor neurons, leading to paralysis and eventually death by respiratory failure within 5 years in 90% of patients. Patients with ALS are typically diagnosed between 40 and 70 years of age. Over time, progressive muscle weakness leads to deficits in activities of daily living (ADL). The pathophysiology of ALS remains incompletely understood, although it involves inflammation. Since edaravone is a free-radical scavenger, the Applicant posits that it may mitigate signs and symptoms of ALS.

2.2. Analysis of Current Treatment Options

There are currently two drugs approved in the United States for treatment of ALS—riluzole and edaravone.

There are multiple formulations of riluzole that have been approved since 1995 in the U.S. All have warnings for neutropenia, interstitial lung disease, and liver injury, and require following serum aminotransferases before and during treatment. Riluzole oral tablet (RILUTEK®) was approved in 1995 as a 50-mg tablet oral twice daily, after studies showed it extended survival (time to tracheostomy or death, p=0.05). Riluzole oral film (EXSERVAN®) was approved in 1995. Riluzole oral suspension (TIGLUTIK®) was approved in 2018 based on bioequivalence to RILUTEK®. The oral formulations of riluzole add oral hypoesthesia to the USPI as an adverse reaction.

Edaravone (RADICAVA®) was approved in 2017 for cyclic intravenous injections. The approval was based on slowing the decline of ALSFRS-R total score over 24 weeks (-5.0 points for edaravone versus -7.5 points for placebo; p=0.0013). The most common adverse reactions with RADICAVA are contusion, gait disturbance, and headache in about 1 in 7 to 10 patients.

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

The following Table is from the Applicant's submission.

Table 1 Regulatory history of oral edaravone

Table 1.2.2-1: Regulatory History Table

Date	Historical Item	Location in Module 1
May 12, 2015	Edaravone received orphan designation for the treatment of ALS	Module 1.12.17
March 15, 2018	The Sponsor received Pre-IND Meeting Preliminary Comments from the Division	Module 1.6.3
April 4, 2019	Type-C Chemistry, Manufacturing, and Controls (CMC) Meeting was held with the Division	Module 1.6.3
July 17, 2019	End of Phase 2 (EOP2) Meeting was held with the Division	Module 1.6.3
October 17, 2019	Fast Track Request was granted	Module 1.7.4
September 2, 2021	The Sponsor received Pre-NDA Meeting Preliminary Comments from the Division	Module 1.6.3
September 8, 2021	Pre-NDA Meeting Preliminary Comment clarifications	Module 1.6.3

Copied from reviewer-guide in this submission

3.2. Foreign Regulatory Actions and Marketing History

RADICAVA oral suspension is not approved in any other country.

Edaravone for intravenous administration (RADICUT) was approved Japan in 2001 for acute treatment of neurological symptoms and functional impairment due to ischemic stroke, and again in 2015 for use in treatment of ALS.

In 2019, the European Medicines Agency (EMA) declined to approve intravenous edaravone, based on concerns with the applicability of Japanese data to the EU population, especially on the survival-related endpoints such as time to tracheostomy and non-invasive ventilation (EMA Withdraw Assessment Report, 2019 May 24).

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

OSIS conducted a remote regulatory assessment (RRA) of the P-One Clinic site of BA Study MT-1186-J03 in Tokyo, Japan from 02/27/2022 to 03/13/2022. The main observations were the discharge of a subject from the inpatient unit for 5 hours one day without a readmission reassessment and changes made to the ICF by the investigator without notifying the IRB. The assessment of the clinical pharmacology reviewer is that the discharge did not affect the bioequivalence assessment. An IR issued by the clinical review team to the Applicant revealed that the change in the ICF was to update the adverse event count from 48 to 53.

Reviewer Comment. These observations did not significantly impact these data.

4.2. Product Quality

Approval with PMC 4266-1: "Provide updated extractable/leachable studies to confirm that the container closure system does not adversely impact the drug product."

4.3. Clinical Microbiology

No issues

4.4. Nonclinical Pharmacology/Toxicology

Rat studies for carcinogenicity assessment were submitted to the RADICAVA NDA and are currently under review.

4.5. Clinical Pharmacology

RADICAVA ORS 105 mg oral suspension formulation is bioequivalent in AUC to the reference RADICAVA 60 mg intravenous formulation (see Clinical Pharmacology Review). However, Cmax was higher for the oral formulation than the IV. See clinical pharmacology review for details.

Reviewer Comment. Long-term safety is being evaluated, and will help assess the clinical impact of long-term exposure to higher Cmax.

4.6. Devices and Companion Diagnostic Issues

Not applicable

4.7. Consumer Study Reviews

Not applicable

5. Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

The primary source of safety data for this review is Phase 3 Study MT-1186-A01, denoted Study A01 in this document. Study MT-1186-J03, referred to as Study J03, is the pivotal bioequivalence study. See Table 2 for the remaining Phase 1 studies. Not listed in Table 2 are two small, ongoing studies of 105 mg of the oral formulation—MT-1186-A02 that has enrolled 3 patients with ALS, and Study MT-1186-A03 that is an extension of Study A01 in patients with ALS who completed Study A01. These interim data are not reviewed.

Table 2 Listing of clinical trials that appear in this review

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Study	Design	Regimen/Schedule/Route	Endpoints	Treatment Duration/Follow Up	No. of patients enrolled
MT-1186-A01 (ALS)	Phase 3 Ongoing Open-label, single-arm	105 mg once daily on the ON-OFF regimen	safety/tolerability; (efficacy endpoints—exploratory)	24 weeks (interim) & 48 weeks	185 E
MCI186-16 (ALS)	*Phase 3 randomized (1:1), double-blind, placebo-controlled,*	*I.V. edaravone 60 mg (or placebo) cycles*	*ALSFRS-R total score change from Baseline to 24 weeks*	*24 weeks*	*206 (102 E + 104 P)*
MCI186-18 (ALS)	*Phase 3 randomized (1:1), double-blind, placebo-controlled*	*I.V. edaravone 60 mg (or placebo) cycles*	*ALSFRS-R total score change from Baseline to 24 weeks*	*24 weeks*	*25 (13 E + 12 P)*
MCI186-19 (ALS)	*Phase 3 randomized (1:1), double-blind, placebo-controlled*	*I.V. edaravone 60 mg (or placebo) cycles*	*ALSFRS-R total score change from Baseline to 24 weeks*	*24 weeks*	*137 in DB phase—69 E + 68 P); 123 in "active phase" OLE (65 E-E + 58 P-E)*
MT-1186-J01 (non-ALS)	Phase 1 randomized, single-blind, placebo-controlled	Oral doses: single of 300 mg; multiple doses up to 200 mg	PK/safety/tolerability	Single- and multiple-dose (5 days once daily)	74 (54 E + 20 P)
MT-1186-J02 (non-ALS)	Phase 1 Clin pharm study including DDI (open-label add-on) and food effect (randomized single-dose cross-over)	Oral Single-dose of 90 to 120 mg	PK/safety/tolerability	Single-dose	83 E
MT-1186-J03 (non-ALS)	Phase 1 Bioequivalence study (randomized, 2 arm, 2-period, 2-seq crossover)	Oral Single-dose: 105 mg oral versus 60 mg IV edaravone	BE/safety/tolerability	Single dose	42 E

MT-1186-J04 (ALS)	Phase 1 open-label Clin pharm study	Oral Single-dose 105 mg oral	PK/safety/tolerability	Single dose	9 E
MT-1186-J05 (ALS)	Phase 1 open-label Clin pharm study in PEG delivery	Oral Single-dose 105 mg oral	PK/safety/tolerability	Single dose	6 E
MT-1186-J06 (non-ALS)	Phase 1 open-label randomized crossover food effect study	Oral Single-dose 105 mg oral	PK/safety/tolerability	5 single doses	16 E
MT-1186-Z-101 (non-ALS)	Phase 1 Bioequivalence study (randomized, 2 arm, 2-period, 2-seq crossover) in NGT vs oral delivery	Oral Single-dose 105 mg oral	PK/safety/tolerability	Single dose	36 E

Abbreviations: E= edaravone group; P=placebo group

5.2. Review Strategy

This review focuses on assessment of the interim safety data from ongoing, Phase 3, open-label Study MT-1186-A01.

6. Review of Relevant Individual Trials Used to Support Efficacy

See clinical pharmacology review.

7. Integrated Review of Effectiveness

See clinical pharmacology review.

8. Review of Safety

8.1. Safety Review Approach

This safety review focuses on the 24-week interim safety data of ongoing, global, single-arm, open-label Study MT-1186-A01 in ALS. The safety assessments in this review are based on the set of all TEAEs (denoted "All Events" in the Applicant's updated safety analyses) in the single open-label arm of Study A01.[1] The placebo group in the IV legacy studies cannot serve as an external control group for Study A01, and a subsection of this review addresses this issue.

Also briefly reviewed are limited safety data summaries from the Phase 1 studies in healthy adults (studies MT-1186-J01, MT-1186-J02, MT-1186- J03, MT-1186-J06, and MT-1186-Z-101) and in patients with ALS (studies MT-1186- J04 and MT-1186-J05) and studies of drug administration by PEG (Study MT-1186-J05) or NGT (Study MT-1186-Z-101). These data are summarized in a single table in this review.

[1] The Applicant's original safety analyses were based on a subset of the TEAEs in Study A01, which were not felt to be from "Normal ALS Progression", contrary to the Division's request at the pre-NDA meeting. Shortly after the NDA submission, an IR was issued to the Applicant to add analyses of All Events to their comparator tables, which was done, and forms the main basis of this review.

8.2. Review of the Safety Database

8.2.1. Overall Exposure

In the oral formulation study MT-1186-A01 (24-week interim), 185 subjects received oral edaravone. Among these, 168 subjects received oral edaravone for at least 6 months (6 cycles). In the IV formulation studies, 184 subjects received IV edaravone (MCI-186), and 184 subjects received placebo. Of the subjects in the IV group, 174 subjects received IV edaravone for at least six months (six cycles).

Table 3 Summary Exposure of Total Treatment Cycles (No. of Cycles)

	Oral Study MT-1186-A01	IV Pooled Placebo-Controlled Studies	
No. of Cycles[a]	MT-1186 105 mg Oral N=185 n (%)	MCI-186 60 mg IV N=184 n (%)	Placebo IV N=184 n (%)
1	185 (100)	184 (100.0)	184 (100.0)
2	183 (98.9)	183 (99.5)	182 (98.9)
3	181 (97.8)	182 (98.9)	179 (97.3)
4	175 (94.6)	182 (98.9)	174 (94.6)
5	170 (91.9)	178 (96.7)	168 (91.3)
6	168 (90.8)	174 (94.6)	167 (90.8)

Abbreviations: IV = intravenous.

[a] Total number of cycles in which subjects received at least one treatment. Each cycle consisted of 28 days. Cycle 1: administration for 14 consecutive days, followed by a drug-free period of 2 weeks, Cycle 2 and after; administration for a total of 10 days per 2 weeks, followed by a drug-free period of 2 weeks.

Source: ISS Table 3.

Table 2.7.4.4-1 in SCS

Reviewer Comment. The oral edaravone exposure is adequate and as previously agreed between the Applicant and Division.

8.2.2. Relevant characteristics of the safety population

The study populations in Study A01 and the legacy IV studies were generally comparable in terms of ALS criteria and concomitant riluzole.

Specifically, in Study A01, subjects were enrolled who had Definite ALS, Probable ALS, Probable laboratory-supported ALS, or Possible ALS according to the El Escorial revised criteria for the diagnosis of ALS; baseline %FVC ≥ 70%; were able to take oral medication; and had ALS symptom onset within 3 years of the time of informed consent. The enrolled population was 64% male with a median age of 61 years (range 22 to 75), and 87% of subjects were on riluzole. All patients were living and functioning independently.

In the IV studies, the USPI indicates that the enrolled ALS population consisted of Japanese

patients (59% male) with ALS and a median age of 60 years (range 29-75). Most (93%) but not all patients were living independently at the time of screening. In the IV (MCI-186) group, 91.3% of subjects (and 90.2% of the placebo group) were on riluzole.

The Applicant pointed out the following differences between these study populations:

1. Patients in Study A01 had a slightly longer disease duration than the IV group—1.6 years versus 1.3 years
2. Study A01 had more patients with FVC<80% than the IV group—25% versus 16%
3. Study A01 excluded patients who were unable to take oral medication, unlike the IV group

Reviewer Comment. These population differences are not significant in terms of this safety review.

8.2.3. Adequacy of the safety database

Adequate

Reviewer Comment. My analyses of the safety datasets of Study A01 are consistent with the Applicant's. The safety database is adequate for this review.

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

None

8.3.2. Categorization of Adverse Events

In Study A01, the definitions of AEs by seriousness, severity, and relationship to investigational drug are adequate.

Categorization of AEs by seriousness, severity, and relationship to ALS progression

The definition of a serious adverse event (SAE) is consistent with 21 CFR 312.32.

The severity of an AE was defined as follows:

a. Mild: The event is transient and easily tolerated by the subject

b. Moderate: The event causes discomfort and interferes with the subject's general condition.
c. Severe: The event causes considerable interference with the subject's general condition and may be incapacitating.

The relationship to drug was either 'no reasonable possibility' (unlikely related to drug; and other factors provide a sufficient explanation) or 'reasonable possibility' (possible relationship to drug; and other factors do not provide a sufficient explanation).

Categorization of AEs by relationship to ALS progression
In Study A01, the AE CRF has an optional checkbox—"Is this event considered part of normal ALS progression?"—with values of Yes (Y), No (N), or Unknown (U), which is captured in the variable AERELALS in the ADAE.xpt dataset. In contrast, the legacy IV studies did not require AEs from normal ALS progression to be recorded.

Consequently, to use the IV placebo group as an external control group for Study A01, the Applicant excludes ALS Progression TEAEs from Study A01 (e.g., excluded TEAEs with AERELALS='Y'). . The Applicant submits tables comparing counts and rates of TEAEs "Excluding Normal ALS Progression" in Study A01 to counts/rates of TEAEs in the IV studies. Shortly after the submission, the Division issued an IR to the Applicant to add a column for All Events of Study A01, regardless of attribution to ALS progression, as requested in the pre-NDA meeting.

Reviewer Comment. The IV placebo group is inadequate to serve as a control group for safety evaluation of Study A01, as follows. The AERELALS checkbox used in Study A01 was optional and therefore unreliable. Although a value of Y is probably a fairly accurate indicator of ALS Progression, values of N and U are not, and U could also mean 'not completed'. Also, the IV legacy studies were conducted a decade earlier, when the standard of care for ALS was different.

8.3.3. Scheduled Clinical Testing

In Study A01, the scheduled clinical testing (Schedule of Procedures) included ECG, hematology, chemistry, urine analysis, %FVC, and C-SSRS, and were scheduled to be collected at all onsite visits (0, 1, 3, 6, 9, and 12 months). Other safety assessment procedures included AE collection, physical exam and vital signs, bodyweight, and others as needed (e.g., pregnancy test). Assessments by telephone were also scheduled between onsite visits, such that safety assessments (onsite or telephonic) occurred every month.

8.4. Safety Results

Quality of Attributions of Adverse Events to Normal ALS Progression. As discussed in 8.1, the attribution of TEAEs to normal ALS progression in Study A01 to establish comparability to the IV placebo group is inadequate. This subsection investigates the quality of these attributions in the data.

Table 4 shows that in Study A01, 68.1% subjects on oral edaravone experienced a non-ALS TEAE (e.g., not attributed to "Normal ALS Progression") compared to 87.5% on IV edaravone, a 20% absolute difference.

Table 4 Overview of TEAE counts in Study A01 among all TEAEs and TEAEs "Excluding Normal ALS Progression"

Table 2.7.4.6-1A Overview of TEAEs – Safety Analysis Population

	Oral Study MT-1186-A01				IV Pooled Placebo-Controlled Studies			
	MT-1186 105 mg Oral N=185				MCI-186 60 mg IV N=184		Placebo IV N=184	
	All Events		Excluding Normal ALS Progression		All Events		All Events	
TEAE Category	n (%)	No. of Events	n (%)	No. of Events	n (%)	No. of Events	n (%)	No. of Events
Any TEAE	146 (78.9)	573	126 (68.1)	369	161 (87.5)	487	160 (87.0)	501
Any TEAE related to IMP	36 (19.5)	60	30 (16.2)	47	19 (10.3)	23	26 (14.1)	30
Any severe TEAE	17 (9.2)	30	10 (5.4)	21	22 (12.0)	31	28 (15.2)	36
Any TESAE	21 (11.4)	24	9 (4.9)	11	32 (17.4)	46	41 (22.3)	60
Any TEAE leading to study treatment discontinuation	11 (5.9)	17	2 (1.1)	6	4 (2.2)	4	10 (5.4)	10
Any TEAE leading to death	6 (3.2)	6	3 (1.6)	3	4 (2.2)	4	2 (1.1)	2

Abbreviations: ALS = amyotrophic lateral sclerosis; IMP = investigational medicinal product; IV = intravenous; TEAE = treatment-emergent adverse event; TESAE = treatment-emergent serious adverse event.
TEAEs related to study treatment based on investigator assessment.
Source: ISS Table 4.1.1, ISS Table 4.1.2.

Applicant's Table 2.7.4.6-1A in Response to IR

Reviewer Comment. The 20% difference in rates is large for group sizes of 185, and alone demonstrates that the the non-ALS progression subset of Study A01 is not comparable to the IV (MCI-186) group. This difference alone supports the inadequacy of the IV placebo group to serve as an external control group for Study A01.

The 204 TEAEs attributed to ALS progression fell into the 13 unique SOCs in Table 5. These SOCs covered 60 unique PT terms (conditions captured by the underlying PT terms appear in parentheses).

Table 5 SOC subject counts for ALS Progression AEs in Study A01

SOC (PT-level conditions)	Subject Count (N=90)
Musculoskeletal and connective tissue disorders (pain, muscle weakness or spasms, and fatigue)	11 (12%)
Respiratory, thoracic and mediastinal disorders (respiratory decompensation)	9 (10%)
Nervous system disorders (ALS signs and symptoms)	8 (9%)
Injury, poisoning and procedural complications (falls, contusions, sprains, and other injuries)	7 (8%)
Gastrointestinal disorders (dysphagia, salivary hypersecretion, and constipation)	5 (6%)
General disorders and administration site conditions (asthenia, fatigue, gait disturbance)	5 (6%)
Investigations (decreased bodyweight or respiratory function)	5 (6%)
Psychiatric disorders (anxiety, depression, insomnia)	4 (4%)
Vascular disorders (hematoma, hypertension)	2 (2%)
Eye disorders (eye hematoma)	1 (1%)
Infections and infestations (oral candidiasis)	1 (1%)
Metabolism and nutrition disorders (decreased appetite)	1 (1%)
Skin and subcutaneous tissue disorders (erythema)	1 (1%)

Source: Reviewer's analysis of the 204 TEAEs in Study A01 with AERELALS='Y'

The 204 ALS Progression TEAEs were individually reviewed, and were consistent with ALS progression. However, many of the TEAEs with AERELALS='N' were also consistent with ALS progression. TEAEs with AERELALS='U' were a mixture of AEs, some consistent and some not consistent with ALS progression. Many patients had TEAEs with any of the three attribution types (Y, N, U)

Reviewer Comment. *The TEAE group "Excluding Normal ALS Progression" included many AEs that appeared to be ALS progression events. This is another reason the IV placebo group cannot serve as a control group for Study A01.*

Riluzole. Since 90% of patients were on riluzole in Study A01 and in the pooled legacy IV studies, some of the AEs in Study A01 may have been from riluzole rather than oral edaravone. For reference, the label for RILUTEK shows the following adverse reactions and their rates (underlined AEs were also observed in Study A01):

1. WARNINGS AND PRECAUTIONS – neutropenia, interstitial lung disease, and elevated serum transaminases
2. ADVERSE REACTIONS in at least 5% of patients – asthenia (19%), nausea (16%), decreased lung function (10%), hypertension (5%), and abdominal pain (5%)

Reviewer Comment. *Riluzole may have explained a number of AEs in Study A01 rather than edaravone.*

8.4.1. Deaths

In ongoing Study A01, there have been 6 deaths (3.2%) among 185 subjects, all convincingly attributable to ALS progression. This rate is comparable to the death rates in the pooled IV legacy studies—edaravone (4/184, or 2.2%) and placebo (2/184, or 1.1%).

Three deaths (subjects (b) (6), (b) (6), and (b) (6)) had the following antecedent SAEs:

1. Pneumonia (Day 121) leading to respiratory failure and death (Day 132)
2. Rapid weight loss (Day 73) and respiratory decline leading to PEG tube placement (Day 106) with postoperative cardiac arrest (Day 106)
3. Completed suicide (Day 149)

These 3 cases were attributed by the investigator to normal ALS progression.

The remaining 3 of the 6 deaths (subjects (b) (6), (b) (6), and (b) (6)), though not flagged as ALS progression events, had antecedent SAEs of respiratory failure or other temporally adjacent AEs consistent with ALS progression.

Reviewer Comment. The 6 deaths in Study A01 appear unrelated to drug.

8.4.2. Serious Adverse Events

In the current RADICAVA label, SAEs are not described (other than hypersensitivity and sulfite allergy in contraindications and postmarket events). In ongoing Study A01, the SAEs likewise do not suggest a significant safety issue at this time.

There were a total of 21 (11.4%) subjects in Study A01 with at least 1 of 24 SAEs (see SAE counts in Table 4), and none were considered drug-related. These SAEs can be summarized as follows:

- 13 subjects with 13 SAEs, all from ALS progression (5 ALS, 3 respiratory failure, 3 dyspnea, 1 weight decreased, 1 gait disturbance)
- 9 subjects with 11 No or Unknown ALS progression SAEs -- 1 atrial fibrillation; 1 pleural effusion; 1 URI; 1 pneumonia (death); 1 restrictive lung disease; 1 resp failure (death); 1 pain, 1 fall, 1 hyponatremia in a patient with autoimmune disease and unknown as to ALS etiology; 1 COVID-19; 1 suicide

- (1 subject was in both ALS groups above, and some SAEs were on the same day)

Reviewer comment. There are no new significant safety issues for oral edaravone suggested by the SAEs in Study A01.

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

In Study A01, 13 (7%) subjects in Study A01 experienced an AE that led to study discontinuation—6 deaths and 7 non-fatal TEAEs. Four of the 7 non-fatal TEAE discontinuations were associated with an SAE. Two of the 7 non-fatal TEAEs were "reasonably related" to therapy, and neither was an SAE—tremor and weakness in extremities.

8.4.4. Adverse Events of Note

Peripheral Neuropathy (PN). The Applicant created this category. As shown in Table 6, it includes the following PTs (spanning 3 SOCs) – hypoesthesia, neuralgia, peripheral neuropathy, paresthesia, muscular weakness, muscle atrophy, and gait disturbance.

Table 6 Applicant's "Peripheral Neuropathy" TEAEs in Study A01

Table 2.7.4.6-23A Summary of Peripheral Neuropathy TEAEs by SOC and PT– Safety Analysis Population

	Oral Study MT-1186-A01		IV Pooled Placebo-Controlled Studies	
	MT-1186 105 mg Oral N=185		MCI186 60 mg IV N=184	Placebo IV N=184
System Organ Class Preferred Term	All Events	Excluding Normal ALS Progression	All Events	All Events
Any TEAE	34 (18.4)	5 (2.7)	30 (16.3)	28 (15.2)
Nervous system disorders	4 (2.2)	3 (1.6)	1 (0.5)	3 (1.6)
Hypoaesthesia	1 (0.5)	1 (0.5)	1 (0.5)	0 (0)
Neuralgia	1 (0.5)	1 (0.5)	0 (0)	0 (0)
Neuropathy peripheral	1 (0.5)	0 (0)	0 (0)	0 (0)
Paraesthesia	1 (0.5)	1 (0.5)	0 (0)	0 (0)
Decreased vibratory sense	0 (0)	0 (0)	0 (0)	2 (1.1)
Sensory disturbance	0 (0)	0 (0)	0 (0)	1 (0.5)
Musculoskeletal and connective tissue disorders	30 (16.2)	2 (1.1)	8 (4.3)	10 (5.4)
Muscular weakness	30 (16.2)	2 (1.1)	8 (4.3)	10 (5.4)
Muscle atrophy	1 (0.5)	0 (0)	0 (0)	0 (0)
General disorders and administration site conditions	2 (1.1)	0 (0)	23 (12.5)	17 (9.2)
Gait disturbance	2 (1.1)	0 (0)	23 (12.5)	17 (9.2)

Abbreviations: ALS = amyotrophic lateral sclerosis; IV = intravenous; PT = Preferred Term; SMQ = Standardised MedDRA Query; SOC = System Organ Class; TEAE = treatment-emergent adverse event.

MedDRA version 23.0. Includes AEs in the Peripheral neuropathy SMQ (narrow and broad). A subject reporting more than 1 TEAE for a particular PT or SOC is counted only once for that PT or SOC.

Source: ISS Table 4.17; ISS A-Table 4.17.

From Table 2.7.4.6-23A in Applicant's Response to IR (01/13/2022)

Reviewer Comment. Most of these TEAEs involved expected motor manifestations of ALS. However, a few were sensory (1 hypoesthesia, 2 paresthesia). One of the sensory cases was foot hypoesthesia in a patient with Type 2 diabetes mellitus. Another was tingling lips in a patient with dysphagia. Another was foot paresthesia in a patient with multiple falls and

injuries. As these few sensory cases have alternative explanations other than ALS or edaravone, there appears to be no causal relationship between edaravone and sensory neuropathy.

Muscular weakness AEs in Study A01 and gait disturbance AEs in the IV studies likely overlap. For example, a fall could be coded as fall, gait disturbance, muscular weakness, or even contusion by different investigators.

Cardiac. In Study A01, 8 (4.3%) subjects experienced at least one AE under the SOC of "Cardiac Disorders", evenly distributed among tachyarrhythmia, sinus, supraventricular, PVCs, Afib, and 1 case of congestive heart failure (CHF). The patient with the CHF event was 71 years of age, and the CHF event was of mild severity; this patient also had TEAEs of Afib and respiratory infections. Eight of the 9 cardiac AEs were identified by a scheduled rather than as-needed ECG. The Afib case was the only SAE among the cardiac events.

In the IV studies, only 2 (1.1%) subjects had a cardiac event, and this is likely related to the IV studies not having had scheduled ECGs.

Reviewer Comment. These data show no new human cardiac safety issue for oral edaravone.

Gastrointestinal Issues (GI) possibly unique to oral administration. These AEs in Study A01 were as follows:

- 24 (13%) subjects had 28 gastrointestinal (GI) AEs (no SAEs)
- Most were not related directly to ALS progression, such as dehydration, decreased appetite, dysphagia, constipation, and others
- 4 subjects had 2 GI TEAEs, and 20 subjects only had 1—suggests no GI issue with the oral product
- Abdominal discomfort/pain in 8 subjects
- Dyspepsia in 2 subjects
- Choking in 1 subject 1
- Oral issues (# subjects): dry mouth (2), oral discomfort/pain (2), throat irritation (1), oral paresthesia (1)
- Diarrhea in 4 subjects
- Oral candidiasis in 1 subject
- GERD in 2 subjects

Reviewer Comment. There are no safety issues in these data specific to an oral compared to an IV product, and riluzole may be associated with a number of these AEs. The GI AEs are relatively few and heterogeneous in Study A01, and do not suggest an oral irritation effect of edaravone.

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

Most Common TEAEs. Table 7 shows counts/rates of the most common TEAEs in Study A01 and the IV studies (and therefore the current USPI).

Table 7 Most common TEAEs in Study A01 (oral) and in the IV label

Safety Analysis Population		Study A01		Legacy IV Studies	
		MT-1186 105 mg oral		MCI-186 60 mg IV	Placebo IV
		N=185	N=185	N=184	N=184
TEAE PT		All Events	Non-ALS	Non-ALS	Non-ALS
Oral: Most Common	Muscular weakness	30 (16.2%)	2 (1.1%)	8 (4.3%)	10 (5.4%)
	Fall	29 (15.7%)	3 (1.6%)	0 (0)	0 (0)
	Fatigue	14 (7.6%)	9 (4.9%)	0 (0)	0 (0)
I.V. Label: Most Common	*Contusion*	*9 (4.9%)*	*6 (3.2%)*	*27 (14.7%)*	*16 (8.7%)*
	Gait Disturbance	*2 (1.1%)*	*0 (0)*	*23 (12.5%)*	*17 (9.2%)*
	Headache	*11 (5.9%)*	*11 (5.9%)*	*14 (7.6%)*	*9 (4.9%)*

Figures were compiled from multiple tables in Applicant's Response to IR (01/13/2022)

Table 7 shows that the top 2 most common PTs in the oral and IV studies are closely related—muscular weakness and fall in Study A01 compared to Contusion and Gait disturbance in the IV studies.

Reviewer Comment. Counts of 0 for Fall (and Fatigue), as well as the considerably higher rate of Gait Disturbance in the IV legacy studies in Japan, suggest between-country differences in coding preferences of these otherwise substantially similar AEs. A fall may result from a gait disturbance or fatigue, or vice-versa. Similarly, fatigue in Study A01 may have been captured as muscular weakness in the legacy IV studies in Japan.

Headache is in the top 3 TEAEs in the IV studies (7.6%), and is already labeled (10%).

Fatigue (7.6%) is in the top 3 TEAEs for Study A01, but is not yet labeled.

Reviewer Comment. The seeming discrepancy in headache rate between the USPI (10%), which was based on the IV studies, and the rate (7.6%) in the IV studies reported in the current submission is not significant. The rates are similar, none of the headaches is an SAE, and headache is still in the top 3 TEAEs for the IV studies. Although it is likely that fatigue was coded as muscular weakness in the IV studies, it is new and therefore should be added to the label. Also, the rate of 7.6% in single-arm Study A01 is hard to interpret absent a concurrent control group, but patients with fatigue issues may benefit from knowing the general magnitude of this rate.

Respiratory, Thoracic, and Mediastinal TEAEs. In Study A01, 32 (17.3%) subjects experienced 42 respiratory events under this SOC. The most frequent were dyspnea (5.4%), cough (3.2%), and respiratory failure (2.2%). The remainder were equally distributed among 19 other upper and lower respiratory events. A total of 9 respiratory events (representing 9 subjects) were SAEs. Respiratory events had a rate of 6%, likely related to lack of reporting of ALS related events in the IV studies.

8.4.6. Laboratory Findings

No new safety concerns were identified.

8.4.7. Vital Signs

No new safety concerns were identified.

8.4.8. Electrocardiograms (ECGs)

No new safety concerns were identified. Eight of the 9 cardiac AEs were identified by scheduled ECG assessment, which were mostly tachyarrhythmias. The IV studies did not have scheduled ECGs.

8.4.9. QT

The Interdisciplinary Review Team (IRT) for Cardiac Safety Studies agrees with the QT labeling proposed by the Applicant, "At exposures (b) (4) 5 times higher than that of the recommended doses of RADICAVA and RADICAVA ORS, edaravone does not prolong the QT interval to any clinically relevant extent."

8.4.10. Immunogenicity

Hypersensitivity and anaphylactic reactions are already in the USPI, based on postmarket case reports from outside of the U.S.

8.5. Safety Analyses by Demographic Subgroups

The Applicant analyzed the safety data from Study A01 by two age groups (<65 years and ≥65 years of age).

Table 8 shows the TESAE counts and rates in Study A01 and the legacy IV studies broken out by age group, and shows an expected increase in ALS-related SAEs with age.

Table 8 TESAEs by Age Group in Study A01

Table 2.7.4.6-19A Summary of Treatment-emergent SAEs by SOC, PT, and Age Group – Safety Analysis Population

	<65 years-old				≥65 years-old			
	Oral Study MT-1186-A01		IV Pooled Placebo-Controlled Studies		Oral Study MT-1186-A01		IV Pooled Placebo-Controlled Studies	
	MT-1186 105 mg Oral N=120		MCI-186 60 mg IV N=131	Placebo IV N=127	MT-1186 105 mg Oral N=65		MCI-186 60 mg IV N=53	Placebo IV N=57
System Organ Class Preferred Term	All Events	Excluding Normal ALS Progression	All Events	All Events	All Events	Excluding Normal ALS Progression	All Events	All Events
Any TESAE	12 (10.0)	7 (5.8)	19 (4.5)	24 (18.9)	9 (13.8)	2 (3.1)	13 (24.5)	17 (29.8)

Table 2.7.4.6-19A in-Applicant's Response to IR (01/13/2022)

Table 8 shows that 21 (11.4%) subjects (=12+9) in Study A01 had at least one TESAE, and that the TESAE rate was slightly higher (13.8%) in the ≥65 year group than in the <65 year age group (10%).

There were no significant, unexpected, age-related safety issues with oral edaravone.

8.6. Specific Safety Studies/Clinical Trials

Table 9 summarizes the safety results from the individual Phase 1 studies in healthy subjects and patients with ALS, excluding Study MT-1186-A01.

Table 9 Summary of Safety Results for the Phase 1 studies of oral edaravone

Study	Brief Description (N=# exposed)	Safety Findings
MT-1186-J01 (non-ALS)	Phase 1 SAD/MAD 100 mg to 200 mg. N=60	No SAEs. 2 TEAEs—headache, conjunctivitis (led to D/C, unrelated to drug)
MT-1186-J02 (non-ALS)	Phase 1 Clin pharm study of 90 mg to 120 mg; including DDI (open-label add-on) and food effect. N=83	No SAEs. No D/Cs. 5 (16%) had AEs when rosuvastatin added (4 diarrhea and 1 transaminase increase—also associated with rosuvastatin)
MT-1186-J03 (non-ALS)	Phase 1 Bioequivalence study. 60 mg IV over 1 hour. 105 mg oral single dose. N=42	No SAEs, D/Cs, or TEAEs related to drug. Mild AST increase in 1 subject (unrelated)
MT-1186-J04 (ALS)	Phase 1 open-label Clin pharm study of single -dose 105 mg. N=9	No SAEs, D/Cs, or TEAEs related to drug. 1 blood in urine (unrelated)
MT-1186-J05 (ALS)	Phase 1 open-label Clin pharm study of single-dose 105 mg in PEG delivery. N=6	5 TEAEs in 3 subjects--unrelated. 1 SAE/death of Worsening of ALS [respiratory depression]--unrelated.
MT-1186-J06 (non-ALS)	Phase 1 open-label randomized crossover food effect study of 105 mg. N=16	No SAEs, D/Cs, or TEAEs related to drug.
MT-1186-Z-101 (non-ALS)	Phase 1 Bioequivalence study of 105 mg. NGT vs oral delivery. N=36	No SAEs, D/Cs, or TEAEs related to drug.

No unexpected or new adverse events or general safety/tolerability issues were apparent from the Phase 1 studies as compared to Study A01.

8.7. Additional Safety Explorations

8.7.1. Human Carcinogenicity or Tumor Development

Not addressed in already approved or new proposed USPI.

8.7.2. Human Reproduction and Pregnancy

No change from current label. The proposed USPI states in Section 8.1 Pregnancy: "There are no adequate data on the developmental risk associated with the use of RADICAVA in pregnant

women."

8.7.3. Pediatrics and Assessment of Effects on Growth

Not applicable

8.7.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Not addressed in the existing USPI.

8.8. Safety in the Postmarket Setting

8.8.1. Safety Concerns Identified Through Postmarket Experience

There are no safety concerns raised by the postmarket experience with approved [intravenous] RADICAVA in the U.S. However, Section 6.2 (Postmarketing Experience) of the USPI for RADICAVA reports "hypersensitivity reactions and anaphylaxis" from post-approval use outside the U.S. Such reactions were not observed in Study A01 or the pre-market setting.

8.8.2. Expectations on Safety in the Postmarket Setting

No concerns

8.8.3. Additional Safety Issues From Other Disciplines

N/A

8.9. Integrated Assessment of Safety

Study A01 was used to assess safety. No new safety concerns were identified during this review, except for fatigue (7.6%), which does not appear in the current USPI.

9. Advisory Committee Meeting and Other External Consultations

Not applicable.

10. Labeling Recommendations

10.1. Prescription Drug Labeling

See final approved labeling.

10.2. Nonprescription Drug Labeling

Not applicable

11. Risk Evaluation and Mitigation Strategies (REMS)

Not necessary

12. Postmarketing Requirements and Commitments

Not necessary

13. Appendices

13.1. References

None

13.2. Financial Disclosures

Covered Clinical Studies: Studies MT-1186-A01, MT-1186-J03, and MT-1186-J05

There are no clinical investigators with disclosable financial interests, including equity interests in the Sponsor as defined by 21 CFR 54.2(b) and significant payments of other sorts as defined by 21 CFR 54.2(f). There were 255 investigators (241 in A01; and 14 in J03 and J05), and none were employees of Applicant.

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/s/

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