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RESEARCH**

APPLICATION NUMBER:

209176Orig1s000

SUMMARY REVIEW

Division Director Summary Review for Regulatory Action

Date	(electronic stamp)
From	Eric Bastings, MD, Deputy Director, Division of Neurology Products
Subject	Division Director Summary Review
NDA/BLA #	209176
Supplement #	
Applicant	Mitsubishi Tanabe Pharma Group
Date of Submission	June 16, 2016
PDUFA Goal Date	June 16, 2017
Proprietary Name / Non-Proprietary Name	Radicava (edaravone)
Dosage Form(s) / Strength(s)	Intravenous injection, 60 mg (30 mg/100 mL)
Applicant Proposed Indication(s)/Population(s)	Amyotrophic lateral sclerosis (ALS)
Action/Recommended Action for NME:	Approval
Approved/Recommended Indication/Population(s) (if applicable)	Treatment of amyotrophic lateral sclerosis (ALS)

Material Reviewed/Consulted	Names of discipline reviewers
OND Action Package, including:	
Project Manager	Jack Dan
Medical Officer Review	Chris Breder
Statistical Review	Tristan Massie
Pharmacology Toxicology Review	David Carbone
OPQ Review	Dan Berger
Microbiology Review	Eric Adeeku
Clinical Pharmacology Review	Xinning Yang
OPDP	Aline Moukhtara
OSI	Cara Alfaro
CDTL Review	Nick Kozauer
OSE/DMEPA	Ebony Whaley
OSE/DRISK	Robert Pratt
CSS	Katherine Bonson
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OPQ/OPF/DIA	Aditi Thakur
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OND=Office of New Drugs

OPQ=Office of Pharmaceutical Quality

OPDP=Office of Prescription Drug Promotion

DMEPA=Division of Medication Error Prevention and Analysis

DRISK=Division of Risk Management

OSE= Office of Surveillance and Epidemiology

CDTL=Cross-Discipline Team Leader

OSI=Office of Scientific Investigations

DEPI= Division of Epidemiology

Division Director Summary Review for NDA 209176 (edaravone)

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1. Benefit-Risk Assessment

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Benefit-Risk Summary and Assessment

Benefit-Risk Summary and Assessment

Amyotrophic lateral sclerosis (ALS) is a fatal degenerative disease that affects both upper and lower motor neurons, leading to gradual muscle weakness with related deficits in activities of daily living. The majority of patients die within 2-4 years of diagnosis. The pathophysiology of ALS remains poorly understood. Riluzole, the only FDA-approved treatment for ALS, provides limited benefit to patients.

The applicant presents edaravone as a free radical scavenger that may counter the oxidative damage hypothesized to occur in the nervous system of ALS patients.

After negative results of the initial 24-week double-blind and placebo-controlled pivotal study in ALS (Study 16), the applicant conducted a post hoc analysis of that study that identified a subgroup of patients with a milder phenotype and shorter time since diagnosis that may respond to edaravone. The applicant applied the post hoc analysis selection criteria to the population of their second pivotal 24-week study (Study 19), which was also double-blind and placebo-controlled. In both Study 16 and Study 19, patients were randomized 1:1 to receive edaravone 60 mg or placebo administered intravenously in treatment cycles (Cycle 1 involved receiving 14 days of treatment followed by 14 days with no treatment, with subsequent cycles alternating between treatment on 10 out of 14 days followed by 14 days with no treatment). The primary endpoint in both studies was the change between baseline and the end of the study (Week 24) in ALS Functional Rating Scale–revised (ALSFRS-R) score. The ALSFRS-R is a questionnaire-based scale that assesses the ability of patients to perform activities of daily living (ADLs). Scores range from 0 (worst) to 48 (normal). The ALSFRS-R is well accepted, and has been used in most recent studies in ALS.

Study 19 demonstrated a highly statistically significant ($p=0.0013$) difference of 2.5 points between edaravone ($n=69$) and placebo ($n=68$) on the ALSFRS-R. This finding is supported by multiple sensitivity analyses. A 2.5 point difference in ALSFRS-R score is clearly clinically meaningful, as each 1-point score change reflects a functional change. In addition, an analysis of the distribution of score changes between baseline and Week 24 indicates that more patients who received edaravone were relatively stable in their ADLs during the course of the study. Although not statistically controlled for multiple comparisons, the results of several secondary endpoints were consistent with the primary efficacy results. Applying a high degree of flexibility, which I consider justified by the great unmet medical need for ALS, I conclude that Study 19 provides substantial evidence of effectiveness.

There are, however, important questions left unanswered by the edaravone development program. First, there is no evidence that edaravone

has any effect on survival. Second, there are reasons to believe that edaravone’s efficacy may decline with increasing disease severity. Unfortunately, it is impossible to determine, on an individual basis, whether edaravone is providing benefit, so that it would not be appropriate to limit the use of edaravone to patients who match the inclusion criteria of Study 19. Third, absent any interaction with FDA during the development program of edaravone, there was essentially no dose-finding conducted by the applicant, and no justification for the peculiar dosing regimen used and proposed by the applicant. Absent other data, that dosing regimen should be recommended in labeling on an empirical basis, but I strongly recommend requesting a commitment from the applicant to conduct a postmarketing study to address the important issue of dose-response.

There are no significant safety signals of concern with edaravone. There were no apparent imbalances between edaravone- and placebo-treated patients with respect to deaths, serious adverse events, or discontinuations related to adverse events. In addition, the profiles of common treatment-emergent adverse events, laboratory abnormalities, and vital sign assessments were also similar between edaravone- and placebo-treated patients. The postmarketing safety database from foreign countries indicates a risk of hypersensitivity and anaphylaxis with edaravone treatment.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	<ul style="list-style-type: none"> ALS is a fatal neurodegenerative disease that affects both upper and lower motor neurons. Patients are typically diagnosed between 40 and 70 years of age, and experience progressive muscle weakness and atrophy, with death generally occurring within 2-4 years of diagnosis, as a result of respiratory muscle involvement. 	ALS is a serious and life-threatening disease that results in death, generally within 2-4 years of diagnosis.
Current Treatment Options	<ul style="list-style-type: none"> Riluzole is the only FDA-approved treatment for ALS. Riluzole only provides a modest benefit to patients. 	There is a clear need for more effective therapies for ALS.
Benefit	<ul style="list-style-type: none"> In two 24-week randomized, placebo-controlled efficacy studies conducted by the applicant, patients were randomized 1:1 to receive edaravone 60 mg or placebo, administered intravenously in treatment cycles. The first cycle involved receiving 14 days of treatment (in 60-minute infusions) followed by 14 days with no treatment; subsequent 	This application has established that edaravone is effective for the treatment of patients with ALS, based on the results of Study 19.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<p>cycles alternated between treatment on 10 out of 14 days, followed by 14 days with no treatment.</p> <ul style="list-style-type: none"> • The primary endpoint in both studies was the change between baseline and the end of the study (Week 24) in ALS Functional Rating Scale–revised (ALSFRS-R) score. The ALSFRS-R is a 48-point questionnaire-based scale that assesses the ability of patients to perform activities of daily living (ADL). • Study 16, the initial pivotal efficacy study, was negative. The applicant, however, conducted a post hoc analysis that identified a subgroup of patients with a milder phenotype and shorter time since diagnosis that may respond to edaravone. • Based on that hypothesis, the applicant conducted Study 19 in the population of patients identified for the first study post hoc subgroup analysis. Study 19 demonstrated a highly statistically significant ($p=0.0013$) difference of 2.5 points on the ALSFRS-R between edaravone ($n=69$) and placebo ($n=68$). This finding was supported by a variety of sensitivity analyses. Although not statistically controlled for multiple comparisons, the results of several secondary endpoints were consistent with the primary efficacy results. • A 2.5 point difference is clinically meaningful, as each 1-point score change on the ALSFRS-R reflects a functional change. In addition, an analysis of the distribution of score changes between baseline and Week 24 supports that more patients on edaravone than on placebo were relatively stable in activities of daily living functional abilities during the course of the study. • There are reasons to believe that edaravone efficacy may decline with increasing disease severity. • There is no established effect of edaravone on survival. 	

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<ul style="list-style-type: none"> • Dose-response has not been adequately assessed by the applicant. 	
Risk	<ul style="list-style-type: none"> • There are no significant safety signals of concern with edaravone. There was no significant imbalance between edaravone and placebo with respect to deaths, serious adverse events, or discontinuations related to adverse events during the studies. In addition, the profiles of common treatment-emergent adverse events, laboratory abnormalities, and vital sign assessments were similar between edaravone and placebo. Postmarketing data from foreign countries indicate a risk of hypersensitivity reactions and anaphylaxis with edaravone treatment. 	The safety profile of edaravone is acceptable for the proposed indication.
Risk Management	<ul style="list-style-type: none"> • There are no safety signals of concern that would warrant any special risk management strategy. 	Risk management can be achieved through product labeling and routine postmarketing surveillance.

2. Background

This application under review is for edaravone, a new molecular entity proposed for the treatment of amyotrophic lateral sclerosis (ALS). Edaravone has been marketed for some time in Japan and a few other Asian countries for the treatment of acute ischemic stroke, [REDACTED] (b) (4) [REDACTED] and has been more recently (2015) approved in Japan and South Korea for the treatment of ALS.

There is a considerable unmet medical need for ALS, as the only drug approved, riluzole, has only been shown to provide a modest benefit to patients.

Edaravone is described by the applicant as a free radical scavenger intended to counter the oxidative damage that occurs in the nervous system of ALS patients of edaravone.

The applicant conducted three randomized controlled studies in patients with ALS. The first one, Study MCI186-16 (described as Study 16 in this document), had overall negative results, but post hoc subgroup analyses suggested a benefit in patients with milder phenotypes and a shorter time since diagnosis. That hypothesis was the basis for the design of the second study (Study MCI186-19, described as Study 19 in this document), which was a randomized, double-blind, 6-month, placebo-controlled trial conducted in the population identified in the subgroup analysis of Study 16. The applicant also conducted a randomized controlled study in patients with more advanced disease (Study MCI186-18), at the request of the Japanese health authorities.

It is important to note there was no opportunity afforded to FDA to provide input into the development program of edaravone, as the initial interaction with the applicant took place only after the above-mentioned efficacy studies had been conducted.

3. Product Quality

I concur with the conclusions reached by the chemistry reviewer regarding the acceptability of the manufacturing of the drug product and drug substance for edaravone. Manufacturing site inspections were acceptable. Stability testing supports an expiry of 36-month when stored at a controlled room temperature in the intended commercial packaging. There are no outstanding product quality issues.

4. Nonclinical Pharmacology/Toxicology

I concur with the conclusions reached by the nonclinical review team that there are no outstanding pharmacology/toxicology issues that preclude approval.

Toxicities observed in animal studies include transient CNS signs (e.g., sedation and hypoactivity), decreases in weight gain, and hematologic signs of regenerative anemia.

Also observed in both dogs and monkeys was central and peripheral nerve fiber axonal degeneration with edaravone administered as a 24-hour continuous IV infusion. Similar effects were not observed with IV boluses or 1-2 hour IV infusions in dogs. Nonclinical data suggest that the degeneration may be reversible, although complete recovery was not observed after 13 weeks. The mechanism by which edaravone may induce nerve fiber degeneration in animals remains unclear, but a possible role of vitamin B6 deficiency was suggested. As edaravone is not to be administered as a continuous infusion for clinical use, the findings are not clearly relevant to humans. In addition, no increased incidence of adverse events related to neuropathy was observed in clinical studies, with the caveat that this may be easily missed a population of ALS patients. Routine postmarketing surveillance for peripheral neuropathy should be adequate to address this risk.

Adverse effects of edaravone were observed in embryofetal development studies. These include decreases in fetal body weight, delays in markers of development, and increased fetal death. A no-effect dose for embryofetal developmental toxicity was not identified, as the lowest toxic dose was less than the recommended human dose of 60 mg, on a body surface area basis. That information should be described in labeling.

Edaravone was negative in a standard battery of genetic toxicology studies. Regarding the assessment of carcinogenicity, the applicant submitted published lifetime carcinogenicity studies of edaravone in mice and rats conducted by the National Cancer Institute (NCI), and requested a waiver for additional carcinogenicity studies. Although there were no indicators of carcinogenicity, the results of the NCI studies are not considered reliable by the review team, because of a lack of toxicokinetic data, and an inadequate number of control animals. The nonclinical review team recommends that adequate carcinogenicity studies in two species be requested post-marketing. I concur.

5. Clinical Pharmacology

I concur with the conclusions reached by the review team from the Office of Clinical Pharmacology (OCP) that there are no outstanding clinical pharmacology issues that preclude approval.

The OCP review team notes that the maximum plasma concentration of edaravone was reached by the end of infusion, and that there was no accumulation of edaravone after multiple dosing. The terminal half-life of edaravone is 4.5 to 6 hours.

Edaravone is extensively metabolized and excreted mainly as glucuronide and sulfate conjugates. Therefore, it is possible that edaravone exposure may be increased in patients with hepatic impairment. The OCP review team concludes that the applicant's proposed dosing regimen can be used in patients with mild and moderate hepatic impairment. However, the OCP team cannot make dosing recommendations in patients with severe hepatic impairment based on available information, and recommends that a study of edaravone in patients with severe hepatic impairment be conducted as a postmarketing requirement. I support that recommendation.

Edaravone and its metabolites are excreted into urine, accounting for at least 70% of the administered dose, with about 1% as unchanged drug. The team also notes that, as the

glucuronide and sulfate conjugate metabolites are inactive, and as there is negligible elimination of edaravone into urine as parent drug, no significant impact of renal impairment on edaravone pharmacokinetics is expected. Therefore, a study of edaravone in patients with renal impairment is not needed to inform labeling, and no dose adjustment is needed in patients with renal impairment.

In addition, as all efficacy studies were conducted in Japanese patients, it was important to assess whether racial differences exist in edaravone pharmacokinetics. Population PK analyses conducted by the applicant support an absence of such differences. Population PK analyses also indicate that the pharmacokinetics of edaravone are not affected by gender, age, or weight.

The review team finds that edaravone has a low potential for significant drug-drug interactions, and edaravone and its metabolites are not anticipated to inhibit major CYP enzymes or transporters. Importantly, there is no concern that edaravone may impact the pharmacokinetics of riluzole, the sole drug currently approved for the treatment of ALS.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical-Efficacy

The ALS clinical development program included a Phase 2 open-label exploratory study (Study MCI186-12, described as Study 12 in this document) and two randomized placebo-controlled efficacy studies (Study 16 and Study 19). Patients who participated in Study 16 were rolled over into Study MCI186-17 (described as Study 17 in this document), in which patients who received edaravone in Study 16 were re-randomized to edaravone or placebo, while all patients who received placebo in Study 16 were switched to edaravone. The applicant also conducted a randomized placebo-controlled study in 25 patients with more advanced ALS (Study 18).

All studies were conducted in Japan.

Study 12

Study 12 was a Phase 2, open-label, exploratory study in patients with ALS. In Study 12, 5 patients were administered 6 cycles of edaravone 30 mg/day, and 14 patients were administered 6 cycles of edaravone 60 mg/day (which is the dose approved in Japan for the treatment of acute ischemic stroke). The first cycle consisted of 2 weeks of daily infusion of study drug followed 2 weeks without treatment. The following cycles consisted of 10 daily infusions of edaravone over a 2-week period, followed by 2 weeks without treatment. Based on results from that study, the applicant selected 60 mg/day (IV infusion over 60 minutes) as the dose to be tested in all Phase 3 studies, following the same dosing regimen as in Study 12.

It is important to note that there is no rational scientific basis for the dosing paradigm used and proposed by the applicant, or for the 60 mg dose proposed by the applicant, except that it is the regimen that was used in studies to support approval of the acute ischemic stroke indication in foreign countries. In particular, there is no justification for the 2-week drug-free period in each treatment cycle, during which no drug pharmacodynamic activity can be expected, based on edaravone's pharmacokinetics. There is also no justification, based on safety concerns or pharmacokinetic considerations, for drug-free periods.

In addition, there was essentially no dose-finding for efficacy conducted by the applicant in the ALS development program. In particular, Study 12, because of its open-label design, duration, and sample size, was merely able to provide limited tolerability information, and no useful information about possible efficacy of the drug came from that study.

Study 16

Study 16 evaluated ALS patients Grade 1 and 2 (based on Japanese staging criteria, i.e., independent living, with or without being able to work) with forced vital capacity (FVC) values greater than 70% of predicted, and a diagnosis of definite ALS, probable ALS, or probable laboratory-supported (according to the ALS El Escorial Revised Airlie House criteria) within 3 years of screening. Patients were randomized 1:1 to edaravone or placebo, to be administered in six treatment cycles of 4 weeks duration (i.e., for a total of 6 months), as described above for Study 12.

The primary efficacy endpoint was the change in the revised ALS functional rating scale score (ALSFRS-R) from baseline to the end of Cycle 6 of treatment (i.e., Week 24). As discussed by the team, the ALSFRS-R is a 48-point questionnaire-based scale that assesses the ability of patients to carry out activities of daily living (ADL). The scale rates 12 functional domains,¹ and has a maximum score of 48, with higher scores indicating better function.

There was no significant difference between edaravone (n=101) and placebo (n=104) in Study 16 (ALSFRS-R score change of -6.35 for placebo and -5.70 for edaravone, p=0.41 according to the applicant's analysis).

After the study failed, the applicant conducted post hoc exploratory analyses of Study 16, and identified a subgroup of patients in which patients who received edaravone declined less on the ALSFRS-R scale than those who received placebo. The post hoc subgroup consisted of 104 patients (50 patients on placebo and 54 patients on edaravone) who had a better functional status at baseline (defined by a score of 2 and better in each individual item of the ALSFRS-R at baseline, and FVC greater than 80%) than the overall study population. In that subgroup, the ALSFRS-R declined 7.1 points for patients on placebo, and 4.9 points for patients on edaravone (nominal p-value of 0.036 according to the applicant).

The applicant further refined the subgroup by limiting it to patients who were within 2 years of ALS diagnosis (instead of within 3 years for the overall study population), and had "definite" or

¹ Speech, salivation, swallowing, handwriting, cutting food, dressing and hygiene, turning in bed, walking, climbing stairs, orthopnea, and respiratory insufficiency. Each item is rated 0 to 4 (with 4 being better).

“probable” ALS diagnoses (excluding patients with probable laboratory-supported ALS). In that more restricted subgroup (29 on placebo and 39 patients on edaravone), the change in ALSFRS-R was -7.59 point for placebo and -4.58 points for edaravone, with a nominal p value of 0.027 for the statistical comparison between the groups, according to the applicant. Notwithstanding the type-1 error with a post hoc analysis of a failed study, Dr. Massie, statistical reviewer for the application, questions the accuracy of that p-value, primarily because of apparent non-normality of data. In addition, in patients not meeting the criteria used to define the post hoc subgroup (including the requirement to be within 2 years of diagnosis), ALSFRS-R outcomes were numerically worse for edaravone than for placebo (-6.11 vs. -5.54). This observation raises considerable doubt on the population identified by the applicant in the post hoc analysis, as the effect was partially at the expense of patients who were not in the subpopulation identified. In addition, Dr. Massie found that within the subgroup of patients identified by the applicant, the treatment effect, when examined as a function of baseline severity of functional impairment, seemed to increase with increasing baseline severity, when the opposite would be expected if the treatment effect was truly larger in less affected patients. Dr. Massie also notes that in the overall population, treatment differences were inconsistent across quintiles of the baseline ALSFRS-R score, and raises concerns about imbalances between treatment groups introduced by the post hoc selection of patients for factors such as riluzole usage and site of initial symptoms (bulbar or not), which may have an impact on disease progression. Dr. Massie notes that in the population identified for the post hoc analysis, 22% of patients in the placebo group were not treated with riluzole, compared to 8% in the edaravone group. That difference alone may have led to a better outcome in the edaravone group. Based on these various issues, Dr. Massie questions the interpretability of the applicant’s post hoc analyses of Study 16. Dr. Breder and Dr. Kozauer largely agree with Dr. Massie’s conclusions, but believe that the findings can still play a contributory role in the overall evidence of effectiveness of edaravone for the treatment of ALS.

At best, I believe that the post hoc analyses of Study 16 could be considered hypothesis-generating, but Study 16 does not clearly constitute an independent source of evidence of effectiveness, in my opinion. It is also important to note that there was no benefit in survival for edaravone in Study 16, both for the overall population ($p=0.38$), and for the population identified for the post hoc analysis ($p=0.39$).

Study 19

Study 19 was prospectively designed to enroll a patient population matching the post hoc subgroup analysis of Study 16, i.e., categorized as either “Definite ALS” or “Probable ALS” in the El Escorial revised Airlie House diagnostic criteria (excluding patients with probable-laboratory supported ALS, which were allowed in Study 16), at Grade 1 or 2 in the Japan ALS severity classification, scoring ≥ 2 points on each single ALSFRS-R item, with normal respiratory function, and within 2 years of diagnosis. The study used the same treatment regimen as Study 16, with 6 treatment cycles of edaravone or placebo, and used the same primary endpoint, i.e., change in ALSFRS-R from baseline to end of Cycle 6 of treatment (Week 24). The study had a number of secondary endpoints: time to death or certain disease progression (death, disability of independent ambulation, loss of upper limbs function, tracheotomy, use of respirator, use of tube feeding, loss of useful speech), percent FVC, Modified Norris Scale score, Amyotrophic Lateral Sclerosis Assessment Questionnaire (ALSAQ40) score, grip strength, and pinch grip strength.

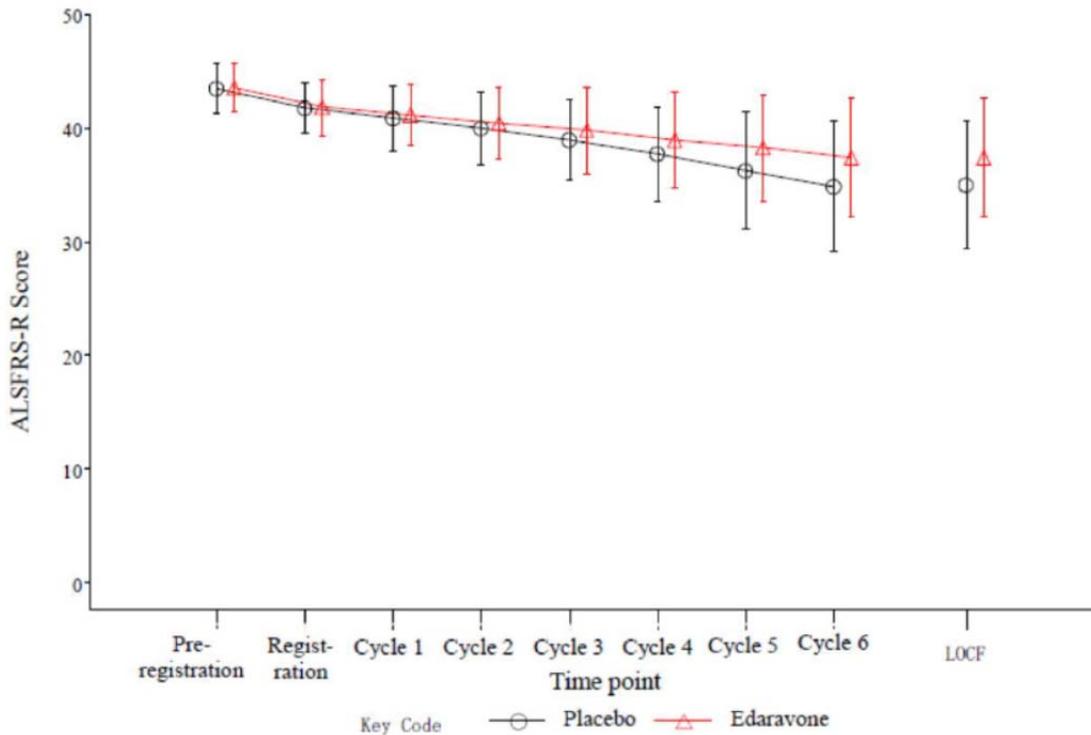
As discussed by Dr. Massie, the final analysis plan of Study 19 stated that no multiplicity adjustment was to be performed because all secondary analyses of the primary endpoint and analyses of the secondary endpoints were exploratory.

After the end of Cycle 6, patients who were willing to continue the study medication were switched to open-label edaravone for six additional treatment cycles (i.e., 24 weeks).

Study 19 randomized 137 ALS patients to edaravone (n=69) or placebo (n=68). Mean disease duration was 1.1 years in both treatment groups, and 91% of patients in both groups were on riluzole. The proportion of patients with initial bulbar symptoms was similar in both groups. The primary endpoint analysis showed a highly significant difference between treatment groups favoring edaravone (ALSFRS-R score change of -6.8 for placebo and -4.4 for edaravone, $p=0.0013$ according to the applicant's analysis, $p=0.0003$ according to the statistical reviewer analysis). The time course of the ALSFRS-R in Study 19 is displayed in

Figure 1. Dr. Massie notes that the prespecified primary analysis with the usual linear term for baseline score was statistically significant and that exploratory polynomial models he used seem to support efficacy over most of the observed range of the baseline ALSFRS-R scores. In addition, a number of sensitivity analyses conducted by Dr. Massie support the robustness of the primary efficacy endpoint results. Moreover, a Wilcoxon test of the joint rank of combined function and survival, an important analysis that we generally recommend for ALS studies, yielded a p value of 0.0009, which supports the meaningfulness of the primary efficacy findings.

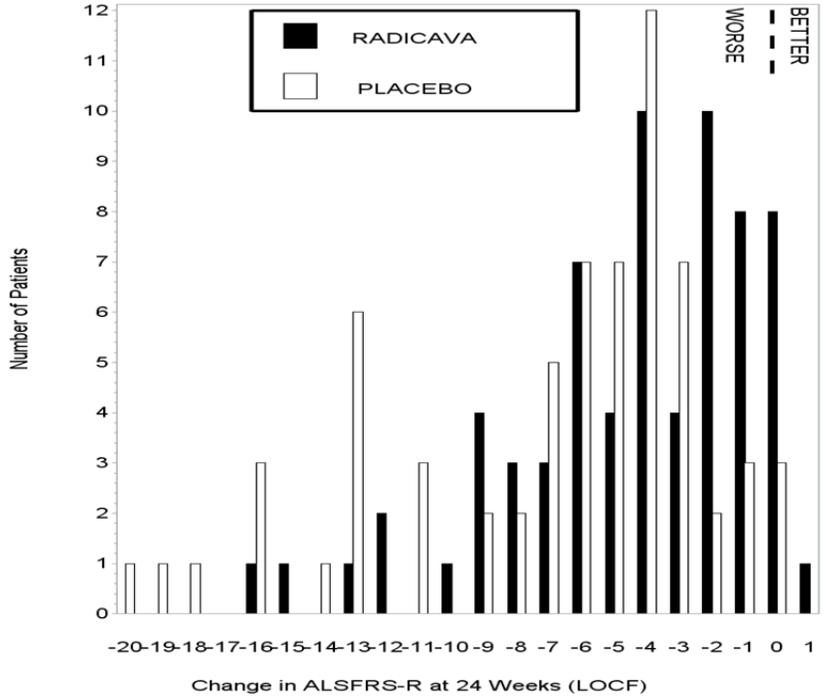
Figure 1: Time course of ALSFRS-R in Study 19 (mean \pm standard deviation) (copied from the statistical review)



Dr. Massie also produced a graph showing the distribution of change from baseline to Week 24 in ALSFRS-R scores in Study 19 (Figure 2). The graph shows that more patients on edaravone

experienced relative stability in ALSFRS-R scores, while more patients on placebo experienced marked declines of ALSFRS-R.

Figure 2: Distribution of Change from baseline to Week 24 in ALSFRS-R Scores in Study 19



As discussed above, there was no plan to address multiple comparisons for secondary endpoints, so I examined the results for nominal significance only. Table 1 summarizes the secondary endpoints results.

Table 1: Efficacy results in Study 19

	Edaravone	Placebo	P value
ALSFRS-R change from baseline (primary endpoint)	-4.4	-6.8	0.0013
Time to death or certain disease progression*			0.13
Percent FVC change from baseline	-16%	-20%	0.09
Modified Norris Scale score change from baseline	-16	-21	0.05
ALSAQ40 change from baseline	+17	+26	0.03
Grip strength change from baseline	-4.08	-4.19	0.86
Pinch grip strength change from baseline	-0.78	-0.88	0.55

*Defined as disability of independent ambulation, loss of upper limbs function, tracheotomy, use of respirator, use of tube feeding, or loss of useful speech.

For the secondary endpoint of time to death or certain disease progression (death, disability of independent ambulation, loss of upper limbs function, tracheotomy, use of respirator, use of tube feeding, loss of useful speech), there was a smaller number of events for edaravone (n=2) than for placebo (n=6), but the difference did not reach nominal statistical significance (p=0.13 to 0.14, depending on the analysis used). There were few events overall, as the study investigated an early ALS population. The individual events are displayed in Table 2.

Table 2: Events involving death or certain disease progression in Study 19 (initial 24 weeks) (copied from statistical review)

Event	Placebo	Edaravone	Total
Death	0	0	0
Disability of independent ambulation	2	0	2
Loss of upper limbs function	0	0	0
Tracheotomy	0	1	1
Use of respirator	0	0	0
Use of tube feeding	1	0	1
Loss of useful speech	3	1	4

For the percent change in FVC from baseline to the end of the study, the results numerically favored edaravone (-16%) over placebo (-20%), but the difference was small, and did not reach nominal significance (p=0.09).

For the Limb modified Norris scale,² results numerically favored edaravone (-12) over placebo (-15), but the difference did not reach nominal significance (p=0.08). For the bulbar component of the modified Norris Scale score, results also favored edaravone (-6) numerically over placebo (-4) (nominal p-value = 0.10). For the combined limb and bulbar scores of the Norris scale, there was a nominally significant difference between edaravone (-16) and placebo (-21), p=0.04 according the applicant, and p=0.052 according to the statistical review.

For the patient-reported outcome ALSAQ40³ score change, there was also a nominally significant difference between the treatment groups favoring edaravone (edaravone 17 point change vs. placebo 26 point change), with a p-value of 0.03.

There were no difference in change of grip strength or pinch grip strength between the edaravone and placebo (nominal p-values of 0.86 and 0.55, respectively).

As noted above, after 24 weeks, patients had the opportunity to be rolled over to active treatment for another 24 weeks (i.e., patients on placebo were switched to edaravone, and

² The Modified Norris Scale consists of two parts, the Limb Norris Scale and the Norris Bulbar Scale. The Limb Scale has 21 items to evaluate extremity function and the Bulbar Scale has 13 items to evaluate bulbar function. Each item is rated in 4 ordinal categories. Higher scores are better on this scale.

³ The Amyotrophic Lateral Sclerosis Assessment Questionnaire (ALSAQ) is a patient-reported outcome with 40 items evaluating physical mobility, activities of daily living and independence, eating and drinking, communication, and emotional reactions. FDA has not reviewed the scale in detail, but, on face, its constructs appears problematic, as described in Dr. Breder's review. Higher scores are worse on this scale.

patients on edaravone continued edaravone). Dr. Massie notes that the proportion of dropouts was substantial for that phase of the study and somewhat different between treatment groups: 24% for edaravone and 45% for placebo. Dr. Massie notes that the applicant reported a nominally significant difference at the end of the active extension (Cycle 12), based on a LOCF analysis. Dr. Massie supplemented the applicant's analysis by a joint rank analysis of ALSFRS-R score and survival time in case of death, which yielded a nominal p-value of 0.052. Dr. Massie also describes that an analysis of death or certain disease progression through Month 12 (which includes 6 months of open-label experience) shows 10 events for edaravone vs. 19 events for placebo (nominal p-value = 0.02). Among these events were 2 deaths in the group originally on placebo, vs. one death for the group originally on edaravone. Dr. Massie emphasizes that these p-value estimates for analyses that cover the open-label extension period are not robust, because of a number of issues that he describes in his review.

Study 17

The applicant also conducted a placebo-controlled extension of Study 16 (under Study 17), in which patients who received edaravone in Study 16 were re-randomized to edaravone or placebo, while patients who received placebo in Study 16 were switched to edaravone. The primary efficacy endpoint was the change in ALSFRS-R from Cycle 7 to 12. That study yielded no useful efficacy information, and I will not discuss it further.

Study MCI186-18

Study MCI186-18 was a randomized, placebo-controlled, exploratory study in 25 patients with more advanced ALS (Japan ALS severity grade 3, which corresponds to "requiring assistance for eating, excretion, or ambulation"). Patients in that study also received study drug for 6 cycles. According to the applicant, the study was performed at the request of the Japan Pharmaceutical and Medical Devices Agency (PMDA). There was no significant difference between treatment groups in ALSFRS-R scores (-6.0 points for placebo and -6.5 points for edaravone, $p=0.83$). Although the study was insufficiently powered to test the primary hypothesis, the fact that results were numerically worse for edaravone is consistent with a lack of efficacy in a more severe population.

Efficacy conclusions

As discussed by Dr. Kozauer, FDA may consider data from one adequate and well-controlled clinical investigation and confirmatory evidence to constitute substantial evidence of effectiveness in support of approval of a marketing application. In addition, in some instances, FDA has relied on a single adequate and well controlled efficacy study to support approval. The characteristics of such studies are described in the FDA's May, 1998, Guidance for Industry on "Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products."

Dr. Breder concludes that Study 19 has many of the features that would be expected for a single study approval, with very persuasive and statistically significant primary endpoint results, and some supportive secondary endpoints. Dr. Kozauer essentially agrees. Dr. Kozauer notes that the ALSFRS-R, used as a primary endpoint in Study 19, is a well-accepted and clinically relevant endpoint for clinical trials in ALS, and that the primary endpoint results are supported by a number of sensitivity analyses. In addition, Dr. Kozauer finds the treatment effect size in Study 19

(2.5-point difference favoring edaravone over a 24-week period) clinically meaningful. Dr. Kozauer also observes that the overall pattern of results on secondary endpoints in Study 19 favored edaravone. Based on these observations, Dr. Kozauer agrees with Dr. Breder that Study 19 provides strong evidence in support of the effectiveness of edaravone for the treatment of ALS. Dr. Kozauer also finds some support in the open-label extension data of Study 19. Dr. Massie, on the other hand, finds the results of Study 19 not very persuasive on their own, because some secondary analyses were not nominally significant (although the study was relatively small).

Regarding the results of Study 16, and in particular of the post hoc analysis conducted by the applicant, Dr. Kozauer acknowledges the many possible reasons that the post hoc subgroup analyses could be misleading, as argued by Dr. Massie. Dr. Kozauer, however, points out that these results were used to generate a hypothesis which was subsequently confirmed, based on the results from Study 19, so that it becomes a matter of judgment as to whether these post hoc analyses from Study 16 can be viewed as confirmatory evidence in support of Study 19. I think that the statements and conclusions from both Dr. Massie and Dr. Kozauer have merit. All agree that Study 19 is a positive study, and all agree on the fact that many, but not all, secondary endpoints of Study 19 showed nominal trends favoring edaravone. There are, however, different views as to whether the post hoc analysis of Study 16 constitutes confirmatory evidence, which Dr. Breder and Dr. Kozauer support, but Dr. Massie finds somewhat circular. On this point, I mostly agree with Dr. Massie, and view the results of the post hoc analysis of Study 16 as primarily hypothesis generating. I also agree with Dr. Breder and Kozauer that the hypothesis was, in fact, verified by Study 19, which obviously gives some credence to a hypothesis that otherwise had serious credibility issues.

As discussed in the Guidance for Industry on “Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products,” whether to rely on a single adequate and well-controlled study is inevitably a matter of judgment. Considering the major unmet medical need for ALS, I find it appropriate in this situation to use a high level of flexibility in applying the standards for demonstrating effectiveness of a new drug. Under this approach, I believe Study 19 can support approval as a single study, primarily based on the very persuasive primary efficacy results. Some support is also provided by secondary efficacy endpoints results, albeit with some weaknesses as discussed above. I also agree with the team that the results of the studies conducted entirely in a Japanese population can be generalized to the US population, for the reasons described in their reviews.

There is a concern from the edaravone development program that treatment benefit may be lost in patients with more advanced disease. In Study 16, the group of patients that did not meet the criteria for less severe disease (of the post hoc analysis) fared numerically worse than placebo, and an exploratory study conducted by the applicant in patients with more advanced disease (Study 18) also showed numerically worse results for edaravone than for placebo. Although these results do not definitely establish that edaravone has deleterious effects in more advanced patients, they certainly raise concern that edaravone efficacy decreases as ALS gets more severe. I agree with Dr. Kozauer that ALS is heterogeneous, and that it would be impossible to identify a precise stage of the disease when treatment benefit may disappear. Therefore, I support an indication not limited to a particular stage of the disease, but the observation of waning treatment benefit is important to mention.

I must also stress that the development program of edaravone, which was unfortunately conducted without FDA consultation, leaves important questions unanswered. In particular, there is no information to determine where the proposed dosing regimen stands with regard to the dose/response, i.e., whether a ceiling of efficacy has been reached. The peculiar dosing regimen, with only 10 days of treatment per month, has no apparent scientific justification, and it is possible, if not likely, that greater benefit may be achieved with more frequent dosing. Again, that question has not been investigated in the development program. Therefore, I strongly recommend a commitment from the applicant to conduct a postmarketing study to address this important issue.

8. Safety

I agree with the review team that the overall subject exposure is sufficient to adequately assess the safety of edaravone. The team describes a total of 349 subjects that received edaravone in the ALS development program, with 306 subjects receiving edaravone for at least 6 months, and 98 receiving edaravone for at least 12 months. In addition, the drug has been marketed in a few Asian countries for several years, and the applicant provided data from the postmarketing safety database from those countries.

As discussed by the team, there were few deaths in edaravone controlled studies in ALS, with a similar rate in placebo- and edaravone-treated patients: 1.1% and 2.2%, respectively. The team notes that these deaths were all related to respiratory failure, the most common cause of death in ALS. Although the small imbalance between groups does not raise a significant safety concern, it is reflective of a lack of benefit of edaravone on survival, at least in the course of the 6-month controlled studies. In the 6-month extension period, the rate of death was again similar for placebo- and edaravone-treated patients (approximately 4%), again denoting an apparent lack of drug benefit on survival.

Dr. Breder notes that, in controlled studies, serious adverse events were overall reported more frequently in placebo-treated patients (22%) than in edaravone-treated patients (17%). There was no serious adverse event that appeared clearly drug-related. Similarly, the rate of discontinuations due to AEs was also numerically higher in placebo-treated patients (5%) than in edaravone-treated patients (2%). Again, no event appeared clearly drug-related.

Common adverse events in placebo-controlled studies are summarized in Table 3.

Table 3: Common adverse events in placebo-controlled studies of edaravone that occurred in at least 5% of the edaravone-treated subjects and at a greater frequency than on placebo (adapted from Dr. Breder's review)

Preferred Term	Placebo (n=184) %	Edaravone (n=184) (%)
Contusion	9%	15%
Gait disturbance	9%	13%
Headache	5%	8%
Eczema	2%	7%
Dermatitis, contact	3%	6%

Gait disturbance was reported at a slightly higher incidence in the edaravone group. This is likely a chance finding (ALS does affect gait, so that event is expected in the study population, and an imbalance between the groups may occur among multiple comparisons). Similarly, the imbalance in the number of events of contusion likely constitutes a chance finding; also, there is no laboratory evidence of a drug effect on coagulation.

There was also a higher incidence of skin-related adverse events in edaravone-treated patients, compared to placebo (26% vs. 20%). The reported skin-related adverse events include eczema (7% vs. 2%), dermatitis contact (6% vs. 3%), rash (4% vs. 2%), and erythema (3% vs. 2%). The fact that an increased incidence of skin-related events across multiple preferred terms was observed suggests this is a drug-related finding. There was also one case of toxic skin eruption on edaravone, considered by the investigator to be non-serious and not severe; the patient withdrew from the study and the event resolved with medical management. The team notes that a detailed description of the toxic skin eruption was not provided by the applicant. None of these events was serious or severe.

Hypersensitivity adverse events, including anaphylactic reactions, have been reported in the postmarketing setting for edaravone. Dr. Breder describes 10 cases that appear causally related to edaravone. These cases include hypersensitivity reactions (redness, wheals and erythema multiforme) and anaphylactic reactions (urticaria, blood pressure decreased and dyspnea). The applicant proposes a description of this information in the Warnings and Precautions section of the labeling, and the review team agrees. I concur.

There were no apparent imbalances in the safety laboratory or vital signs assessments between edaravone and placebo.

The applicant did not submit a REMS or other risk management plan with the application but proposes the use of a Medication Guide as part of the labeling. I do not believe a Medication Guide is justified by the safety profile of edaravone.

Finally, the review team concludes that the safety findings from the Japanese ALS subjects who were enrolled in the clinical trials in this development program are expected to be relevant to US ALS patients. I concur.

Of note, the applicant has not yet conducted a thorough QT (TQT) study. The limited ECG data provided by the applicant did not identify a QT prolongation signal. Considering the unmet medical need in ALS, a TQT study can be deferred to the postmarketing period, but should be requested as a postmarketing requirement (PMR).

9. Advisory Committee Meeting

This application was not referred for review to an advisory committee because the safety profile of edaravone is acceptable for the proposed indication and the clinical trial design is acceptable.

10. Pediatrics

PREA was not triggered for this orphan indication.

11. Other Relevant Regulatory Issues

There are no unresolved regulatory issues.

Six sites of the pivotal efficacy study were inspected by OSI, and were found acceptable.

The Controlled Substance Staff concludes that edaravone does not have abuse potential, and recommends eliminating Section 9 (Abuse and Dependence) from labeling. I concur.

12. Labeling

There are no unresolved labeling issues.

As discussed by Dr. Kozauer, the applicant proposed Warnings and Precautions (b) (4) (b) (4), but these were deleted as there was no scientific justification for these warnings.

13. Postmarketing

I agree with the review team that a risk evaluation and mitigation strategy (REMS) is not necessary for edaravone.

I support the following postmarketing requirements proposed by the review team:

- 1) A TQT study to evaluate the potential for small increases in QT interval (greater than 10 ms).
- 2) A study to evaluate the pharmacokinetic properties of edaravone and its metabolites in patients with severe hepatic impairment (the subjects would not need to be ALS patients).
- 3) Carcinogenicity studies in rat and mouse.

I also recommend a postmarketing study to assess the safety and efficacy of edaravone using a more rational dosing regimen (i.e., daily or near daily), and exploring the dose-response.

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/s/

ERIC P BASTINGS
05/04/2017