CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209176Orig1s000

OFFICE DIRECTOR MEMO

Office of Drug Evaluation-I: Decisional Memorandum

Date	May 4, 2017
From	Ellis F. Unger, MD, Director Office of Drug Evaluation-I, Office of New Drugs, CDER
Subject	Office Director Decisional Memo
New Drug Application (NDA) #	209176
Applicant Name	Mitsubishi Tanabe Pharma Corporation
Date of Submission	June 16, 2016
PDUFA Goal Date	June 16, 2017
Proprietary Name/ Established (USAN) Name	Radicava edaravone injection
Dosage Forms/ Strengths	30mg/100mL
Indication originally sought by applicant	"RADICAVA is (b) (4) indicated for the treatment of Amyotrophic Lateral Sclerosis (ALS)."
Action:	*approval*

Material Reviewed/Consulted - Action Package, including:	
Project Manager	Jack Dan, Susan Daugherty, Jackie Ware
Medical Officer/Clinical	Christopher Breder
Pharmacology Toxicology	David Carbone, Lois Freed
Office of Pharmaceutical Quality	Wendy Wilson, Martha Heimann, Dahlia Woody, Sithamalli Chandramouli, Kasturi Srivasachar, Dan Berger, Kumar Janoria, Edwin Joa, Eric Adeeku, Maotong Zhou, Aditi Thakur, Christina Capacci-Daniel, Banu Zolnik, Mehul Mehta, Erika Pfeiler
Clinical Pharmacology/Pharmacometrics	Xinning Yang, Sabarinath Sreedharan, Dhananjay Marathe, Atul Bhattaram, Kevin Krudys, Mehul Mehta
Rare Disease	Larry Bauer, Lucas Kempf
Office of Biostatistics	Tristan Massie, Kun Jin, Hsien Ming (James) Hung
Office of Prescription Drug Promotion	Aline Moukhtara, Sharon Williams, Marcia Williams
Office of Scientific Investigations	Cara Alfaro, Lakisha Williams, Yolanda Patague, Susan Thompson, Kassa Ayalew
Office of Surveillance and Epidemiology, Office of Pharmacovigilance and Epidemiology/Division of Epidemiology I	Elisa Braver
Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis	Lolita White, Ebony Whaley, Corwin Howard, Todd Bridges, Ruth Maduro
Office of Surveillance and Epidemiology, Division of Risk Management	Robert Pratt, Donella Fitzgerald, Jamie Wilkins Parker
QT Interdisciplinary Review Team	Dhananjay Marathe, Moh Jee Ng, Qianyu Dang, Michael Li, Christine Garnett
Controlled Substance Staff	Katherine Bonson
Associate Director for Labeling	Tracy Peters
Cross-Discipline Team Leader	Nicholas Kozauer
Deputy Director, Division of Neurology Products	Eric Bastings
Director, Division of Neurology Products	Billy Dunn

Reference ID: 4094051

1. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease of upper and lower motor neurons, which leads to progressive muscle weakness and death in the majority of patients within 2 to 4 years of diagnosis. Riluzole, marketed as Rilutek and generics, was approved for the treatment for ALS in 1995, but the Division notes that the drug provides only limited benefit to patients.

The principal evidence of efficacy is from Study 19, an adequate and well-controlled study 24 weeks in duration, with a randomized, double-blind, placebo-controlled design. Patients were randomized 1:1 to receive edaravone (n=69) or placebo (n=68), administered in 6 treatment cycles of 2 weeks, alternating with 2-week treatment-free periods. The drug is administered by the intravenous route.

The 1° endpoint was the ALS Functional Rating Scale–revised (ALSFRS-R) score, assessed as the change between baseline and the end of the 6th treatment cycle (Week 24). The ALSFRS-R is a validated questionnaire-based instrument that assesses 12 activities of daily living: speech, salivation, swallowing, handwriting, cutting food, dressing/hygiene, turning in bed, walking, climbing stairs, dyspnea, orthopnea, and respiratory insufficiency. Each item is scored from 0 (no function) to 4 (normal), for a full range of zero to 48 units.

The study demonstrated a statistically significant difference of 2.5 units (95% confidence interval 1.0, 4.0) in decline of the ALSFRS-R. The applicant's *p*-value was 0.0013, which was corroborated by many alternative and complementary analyses conducted by FDA. Results of several 2° endpoints trended favorably. Although some might consider a treatment effect of 2.5 on a 48-unit scale to be trivial, we believe that it is quite meaningful. Each category in the ALSFRS-R seems clinically important, and because each domain includes only five levels that span 0 (cannot do) to 4 (normal), prevention of even 1 unit of worsening in a single domain seems meaningful and desirable for individuals with ALS.

Patients entered in Study 19 had a mean baseline ALSFRS-R score of 42, which is 6 points removed from being symptom-free. Over 6 weeks, patients in the edaravone group worsened by a mean of 4.4 units, whereas patients in the placebo group worsened by a mean of 6.8 units. Retention of 2.5 units of function (mean) over a 24-week period is clinically meaningful and definitely of value. Moreover, the mean effect does not reflect the value that many patients may receive: an analysis of the distribution of ALSFRS-R score changes shows a fairly impressive shift, indicating better preservation of function with edaravone. Unfortunately, most patients will not be able to determine whether or not they are deriving benefit from the drug; therefore, many will continue it indefinitely, irrespective of benefit.

Study 19 has many of the characteristics of an adequate and well-controlled trial that make it adequate to support an effectiveness claim as a single trial (see Efficacy Conclusions, page 15). I conclude that the study meets the legal standard, providing substantial evidence of effectiveness.

No significant safety signals have been identified, other than risk of hypersensitivity reactions and anaphylaxis (based on foreign postmarketing data). The size of the database is limited, however, and it is possible that serious but uncommon toxicities will arise during marketing. Most patients are likely to choose to undergo placement of a central venous access port, with its attendant risks of complications and infections. We are aware that individuals with ALS will accept significant risk and unknown risk.

Considering all of the above, edaravone's benefits outweigh its known and potential risks, and the NDA will be approved.

Reference ID: 4094051

Dimension	Discussion
Analysis of Condition	ALS is a fatal neurodegenerative disease that affects both upper and lower motor neurons. Patients develop progressive muscle weakness and atrophy, and generally succumb to the disease within 2-4 years of diagnosis with death due to respiratory insufficiency. Onset is typically between 40 and 70 years of age.
Current Treatment Options	Riluzole is the only FDA-approved treatment, indicated "for the treatment of ALS." The Division notes that riluzole provides only modest benefit to patients; therefore, there is a critical unmet need for more effective therapies for patients with ALS.
Benefit	The principal evidence of efficacy is from Study 19, an adequate and well-controlled study, 24 weeks in duration, with a randomized, double-blind, placebo-controlled design. Patients were randomized 1:1 to receive edaravone or placebo, administered in six 2-week treatment cycles (alternating with 2-week treatment-free periods). The drug is administered intravenously. 1° endpoint: The 1° endpoint was the ALS Functional Rating Scale–revised (ALSFRS-R) score, assessed as the change between baseline and the end of the 6th treatment cycle (Week 24). The ALSFRS-R is a validated questionnaire-based instrument, previously used to assess the efficacy of drugs for ALS. The Scale assesses 12 activities of daily living: speech, salivation, swallowing, handwriting, cutting food, dressing/hygiene, turning in bed, walking, climbing stairs, dyspnea, orthopnea, and respiratory insufficiency. Each item is scored from 0 (no function) to 4 (normal), for a full range of zero to 48 units. Results: Study 19 demonstrated a statistically significant difference of 2.5 units on the ALSFRS-R between the edaravone (n=69) and placebo (n=68) groups. The applicant's *p*-value was 0.0013, which was corroborated by many alternative and complementary FDA analyses. Although the Type-I error rate was not controlled for multiple comparisons, the results of several 2° endpoints trended favorably. Meaningfulness: Each category in the ALSFRS-R appears clinically meaningful on its face. And because each domain includes only five levels that span 0 (cannot do) to 4 (normal), prevention of even 1 unit of worsening in a single parameter would seem meaningful and desirable for individuals with ALS. Thus, prevention of 2.5 units of functional loss over a 24-week period is clinically meaningful and definitely of value. An analysis of the distribution of ALSFRS-R score changes shows that more edaravone patients than placebo patients were relatively stable in functional abilities during the course of the study, whereas more patients in the placebo group had substantial functional loss. Discontinuing treatment for lack of effect: As it is with most treatments intended to delay progression of a chronic disease, patients will have little ability to determine whether they are gaining benefit from the drug. In the absence of side effects and complications from vascular access, many patients will opt to continue treatment

Reference ID: 4094051

Dimension	Discussion
	throughout the course of their disease, and will never know whether they in fact benefitted from the drug. Restriction of indication based on disease severity: Although there are some reasons to believe that edaravone's efficacy may decline with increasing disease severity, this is by no means established, and the indication should not limit use to a particular level of disease severity. Survival: There is no established effect of edaravone on survival. Adequate dose: Dose-response has not been adequately assessed by the applicant; a study to assess higher doses will be requested as a postmarketing commitment.
Risk	There are no significant safety signals of concern with edaravone, i.e., there is no evidence of harm, albeit with a limited safety database. Postmarketing data from foreign countries indicates risk of hypersensitivity reactions and anaphylaxis. It is certainly possible that serious but uncommon toxicities will be detected during marketing. Based on the 'rule of three,' with 306 patients exposed for ~6 months and no serious toxicity, it can be concluded with 95% confidence that fewer than ~1 person in 100 will experience serious toxicity within this timeframe. For a treatment for individuals with ALS, significant risk and unknown risk are acceptable. Most patients will likely choose to undergo placement of a central venous access port, with its attendant inconvenience, and risks of complications and infections.
Risk Management	There are no safety signals of concern that would warrant a special risk management strategy. Risk management can be achieved through product labeling and routine postmarketing surveillance.

2. Background

The applicant is seeking marketing authorization for edaravone for the treatment of amyotrophic lateral sclerosis (ALS), which has been designated as an orphan disease. Edaravone is a new molecular entity in the U.S., although the drug has been approved for the treatment of ALS in Japan and South Korea since 2015, and approved in various Asian countries for the treatment of acute ischemic stroke (b) (4) There is a considerable unmet medical need for ALS, as the only drug approved, riluzole, provides only modest benefit to patients.

The applicant represents edaravone as a free radical scavenger, and postulates that the drug may counter oxidative damage in ALS patients. The data, however, are not adequate to support this or any other specific mechanism of action, (b) (4)

The development program was conducted entirely in Japan, without input from FDA, and there are some major gaps in knowledge, particularly with respect to dose-response and the dosing regimen itself (which is unusual). Nevertheless, we encouraged the company to submit an NDA, given what we viewed as promising results from the study in Japan, and in light of the unmet need for new treatments for ALS in the US. All of the pre-submittal regulatory action – from the pre-IND meeting to the pre-NDA meeting – took place in 2015, leading to the submission of the NDA in June, 2016.

Reference ID: 4094051

There are two principal clinical studies. The first study (Study 16) was negative, but various *post hoc* exploratory subset analyses yielded a promising subset of patients with less severe disease in which there was a robust treatment effect,[1] leading to an attempt, ultimately successful, to identify an enriched population for a second study. Thus, Study 19 was a 6-month randomized, double-blind, placebo-controlled trial that enrolled the population identified in the subgroup analysis of Study 16. Study 19 was clearly positive, and is the basis for the approval action.

3. Product Quality

The Office of Pharmaceutical Quality (OPQ) recommends approval of this NDA. There are no significant outstanding manufacturing or facility risks precluding approval. The manufacturing facilities were found to be acceptable.

4. Nonclinical Pharmacology/Toxicology

The application is approvable from a pharmacology/toxicology standpoint. The review found the nonclinical data adequate to support approval of the NDA, with post-marketing requirements (PMR) recommended for carcinogenicity studies in two species. Key conclusions from the pharmacology-toxicology review:

- The applicant's proof-of-concept studies in animal models of ALS (mutant SOD transgenic [H46R] rat) demonstrate minimal, if any, biological effect at edaravone doses of 1.5 to 6 mg/kg IV (1-hr infusion), whereas at least one published study suggests salutary effects. Overall, the evidence seems inconclusive.
- Toxicities include transient CNS signs (e.g., sedation, staggering gait, lethargy), reduced weight gain, and regenerative anemia.
- Central and peripheral nerve fiber axonal degeneration associated with limited limb use was observed in both dogs and monkeys with a 28-day continuous IV infusion of edaravone. Similar effects were not observed with 2-hour IV infusions in dogs. The peripheral nerve fiber degeneration in animals receiving 120 mg/kg/day for 2 weeks was reversible after a 13-week recovery period, whereas nerve fiber degeneration in spinal cord was not reversible. The mechanism by which edaravone may induce nerve fiber degeneration in animals is unknown, but vitamin B6 deficiency was suggested by the applicant. The review notes that because edaravone is not to be administered as a continuous infusion in patients, the findings are not clearly relevant to humans.
- Adverse effects of edaravone were observed in embryofetal development studies. Decreases in fetal body weight were observed at all doses tested. A no-effect dose for embryofetal developmental toxicity was not identified, as the low dose was less than the recommended human dose of 60 mg, on a body surface area basis. This information will be described in labeling.
- Edaravone was negative in a standard battery of genetic toxicology studies. The applicant submitted publications of National Cancer Institute-conducted lifetime carcinogenicity studies in mouse and rat, and requested a waiver for additional studies. Results of these studies are not considered

[1] This finding is somewhat counterintuitive, however, as there is a general expectation that patients with more severe illness would demonstrate a larger effect size. For drugs intended to slow or prevent the progression of a serious disease, however, it is possible that the pathology in patients with more advanced disease will be too severe to ameliorate.

reliable by the review team, however, because the drug was given by the dietary route and there were no toxicokinetic data to verify exposure. The nonclinical review team recommends conduct of additional carcinogenicity studies in two species as a post-marketing requirement, and the required studies will be included in the action letter.

5. Clinical Pharmacology

The Office of Clinical Pharmacology (OCP) recommends approval from a clinical pharmacology perspective.

The following are the chief conclusions of their review:

- Dose selection was based on a study of edaravone in acute stroke that compared 10, 30, and 45 mg/30 minutes, administered twice daily. They found no difference in efficacy between 30 mg BID and 45 mg BID, and thus selected 60 mg QD (the equivalent of 30 mg BID) for their phase 3 study in ALS.
- There was no dose-finding in the ALS development program per se; the daily dose of 60 mg is not well justified.
- The maximum plasma concentration of edaravone was reached by the end of infusion, with no accumulation after multiple dosing. The terminal half-life of edaravone is 4.5 to 6 hours.
- The review is relatively silent with respect to the lack of justification, based on safety concerns or pharmacokinetic considerations, for the 2-week drug-free period within each treatment cycle, during which no pharmacodynamic activity can be expected. Moreover, there is no rationale given for administration 5 days per week (e.g., rather than daily).
- Population PK analyses show that sex, age, and weight have little effect on pharmacokinetics.
- Edaravone is extensively metabolized and excreted mainly as glucuronide and sulfate conjugates.
- For a number of reasons, the OCP review team concludes that the proposed dosing regimen is appropriate for patients with mild and moderate hepatic impairment, but they were unable to make a dosing recommendation for patients with severe hepatic impairment, where edaravone exposure may be increased. The OCP review team recommends a postmarketing requirement to evaluate the impact of severe hepatic impairment on the pharmacokinetics of edaravone; the Division agrees and I concur.
- For several reasons delineated in the OCP review, no dosing adjustment is needed in patients with renal impairment and a renal impairment study is not necessary.
- There is a low potential for drug-drug interactions *in vivo* at the to-be-marketed dose; edaravone and its metabolites are not anticipated to inhibit major CYP enzymes or transporters.
- Because all of the clinical efficacy studies were conducted in Japanese patients, it was important to assess whether differences exist in edaravone pharmacokinetics between US (Caucasian) and Japanese patients. Population PK modeling predicted no differences in AUC or C_{max} between Caucasian and Japanese healthy subjects.
- At therapeutic doses, there is no concern with respect to interactions between edaravone and riluzole, an approved drug widely used for the treatment of ALS in the US.

Reference ID: 4094051

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical – Efficacy

The studies are well summarized in the Division's and statistician's review documents. The clinical development program included an exploratory, open-label, phase 2 study (Study 12), as well as two randomized, double-blind, placebo-controlled studies (Studies 16 and 19). The applicant also conducted a randomized placebo-controlled study in 25 patients with more advanced ALS (Study 18). All studies were conducted in Japan.

The clinical review team in the Division concludes that the applicant has provided substantial evidence of efficacy and supports approval of the NDA. The review team from the Office of Biostatistics is not enthusiastic with respect to approval. They note that there is only one study supporting efficacy (Study 19), pointing out that the *post hoc* subset analysis from the Study 16 is only hypothesis-generating. Their review, furthermore, highlights the limitations of the positive study: the 2° endpoints are not nominally statistically significant, and the study was conducted in Japan. Thus, they question the applicability of the study results to the US population. These issues are discussed in detail below.

Study 12

Study 12 was a Phase 2, open-label, exploratory study in patients with ALS. Patients received 6 cycles of edaravone, with 5 subjects receiving 30 mg/day and 14 subjects receiving 60 mg/day (the latter is the dose approved in Japan for treatment of acute ischemic stroke). The initial cycle consisted of daily infusions for 14 days, followed by 2 weeks with no treatment. Subsequent cycles consisted of 10 daily infusions over a 2-week period, followed by 2 weeks without treatment.

Based on the results from this study, the applicant selected the higher dose (60 mg/day) and the same regimen/schedule for the phase 3 studies. Given its open-label design and limited sample size, however, Study 12 was only capable of providing limited information on tolerability, and no information about efficacy.

Study 16

Study 16 evaluated individuals with Grade 1 and Grade 2 ALS (based on Japanese staging criteria, i.e., independent living, with or without being able to work), with forced vital capacity (FVC) $\geq$ 70% of predicted, and a diagnosis of definite ALS, probable ALS, or probable-laboratory supported ALS (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 for Study 12, above.

The 1° efficacy endpoint was the change in the revised ALS functional rating scale score (ALSFRS-R) from baseline in treatment Cycle 1 to the end of treatment Cycle 6 (i.e., Week 24). As discussed by the Division, the ALSFRS-R is a questionnaire-based scale that assesses the ability of patients to carry out

Reference ID: 4094051

activities of daily living. The instrument rates 12 functional domains from 0 (maximum impairment) to 4 (normal),[2] for a total possible score of 48.

There was no significant difference in ALSFRS-R between the edaravone (n=101) and placebo (n=104) groups. Function worsened in both groups: the ALSFRS-R score change was -5.7 for edaravone and -6.4 for placebo, *p*=0.41, according to the applicant's analysis. Even if this analysis had reached statistical significance, there were a number of problems identified by Dr. Massie that would have undercut the persuasiveness of the study.

The applicant conducted *post hoc* exploratory subgroup analyses from the failed study with the aim of identifying a population in whom edaravone might be effective. They identified a non-prespecified subset of 104 patients (54 edaravone and 50 placebo) who had better functional status at baseline than the overall study population (defined as a score of ≥ 2 on each individual item of the ALSFRS-R and FVC $\geq 80\%$). In that subgroup, the ALSFRS-R declined by 4.9 points for patients on edaravone, and by 7.1 points for patients on placebo (nominal *p*-value for the difference = 0.036 according to the applicant).

The applicant further refined the subset by limiting it to patients who were within 2 years of their ALS diagnosis (instead of within 3 years for the overall study population), and who had "definite" or "probable" ALS diagnoses (excluding patients with probable laboratory-supported ALS). In this more restricted subset (39 edaravone and 29 placebo), the ALSFRS-R worsened by 4.6 points in the edaravone group and 7.6 points in the placebo group; applicant's nominal *p*-value = 0.027.

Aside from the well-recognized limitations of any unplanned subset analysis of a failed study, Dr. Massie identified a number of inconsistencies and issues that further weakened the veracity of the subset finding. The applicant's basic premise – that patients with less severe disease are able to benefit from edaravone whereas those more severely affected are too sick to benefit – is not supported by the totality of the data. Dr. Massie found the following:

- For patients not meeting the subset criteria, the results trended numerically worse for edaravone than placebo (worsening by 6.1 and 5.5 points, respectively). This observation raises concern regarding the validity of the *post hoc* analysis, as the effect in the selected subset was partially at the expense of the unselected patients.
- Within the selected subset, the treatment effect tended to *increase* as baseline disease status *worsened*, a finding that runs counter to the applicant's hypothesis.
- Within the selected subset, there were imbalances between treatment groups for factors such as riluzole usage (92% in the edaravone subset vs. 78% in the placebo subset) and site of initial symptoms (bulbar or not) that may have favored the edaravone subset and accounted for at least some of the apparent treatment effect.
- The applicant's analyses assumed that the data were normally distributed; however, this assumption was not met.

[2] The 12 domains are speech, salivation, swallowing, handwriting, cutting food, dressing and hygiene, turning in bed, walking, climbing stairs, dyspnea, orthopnea, and respiratory insufficiency. Each is rated from 0 to 4: 0 indicates maximum impairment; 4 is normal.

In light of these issues, Dr. Massie strongly questions the interpretability of the applicant's *post hoc* analyses. As explained by Dr. Bastings, Drs. Breder and Kozauer largely agree with Dr. Massie's conclusions, but believe that the findings can nevertheless contribute to the overall evidence of effectiveness of edaravone for the treatment of ALS. Dr. Bastings opines that the *post hoc* analyses could be considered, at best, hypothesis-generating, but do not clearly constitute independent evidence of effectiveness. I believe that Drs. Bastings and Massie have characterized the strength of the data quite well. The data are, at best, hypothesis generating, and should not be construed to constitute independent evidence of efficacy.

Study 19

Study 19 was a double-blind, placebo-controlled, parallel-group investigation prospectively designed to enroll a patient population matching the *post hoc* subset analysis of Study 16. Patients had to be categorized as having "Definite" or "Probable" ALS using the El Escorial revised Airlie House diagnostic criteria (excluding patients with probable-laboratory supported ALS), Grade 1 or 2 using the Japan ALS severity classification, having scores of $\geq$ 2 points on all individual ALSFRS-R items, normal respiratory function, and within 2 years of diagnosis.

As in Study 16, patients were randomized 1:1 to receive 6 treatment cycles of edaravone or placebo, and the 1° endpoint was change in ALSFRS-R from baseline to the end of treatment Cycle 6 (Week 24). There were numerous 2° endpoints: time to death or certain disease progression (death, disability of independent ambulation, loss of upper limb function, tracheotomy, use of respirator, use of tube feeding, loss of useful speech), %FVC, Modified Norris Scale score, ALS Assessment Questionnaire (ALSAQ40) score, grip strength, pinch grip strength, and ALS severity classification. These 2° endpoints were exploratory, with no plan to control the Type-1 error rate.

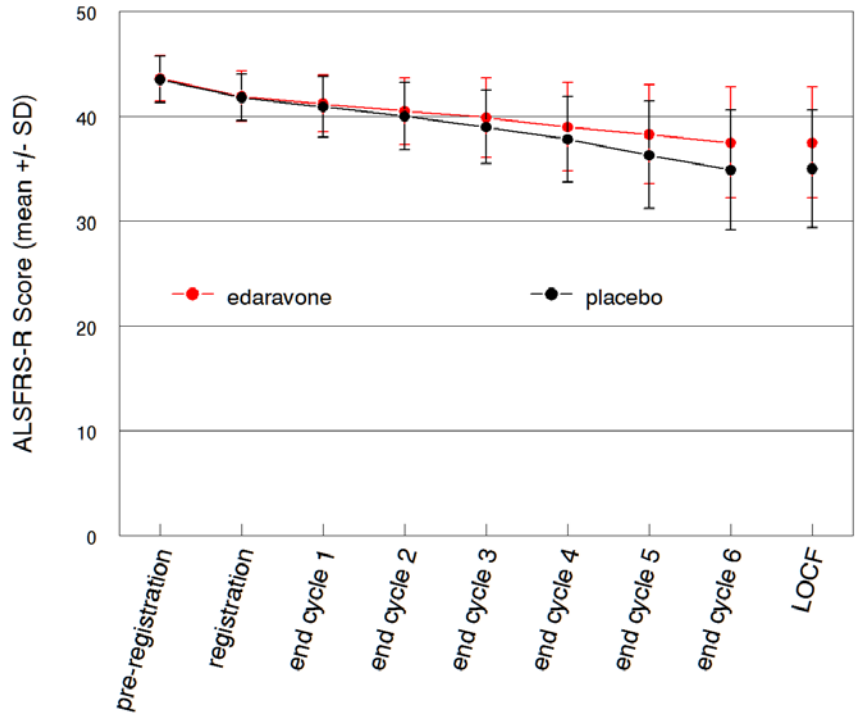
The double-blind portion of the study was carried out between November, 2011 and September, 2014 at 26 sites in Japan. A total of 137 ALS patients were randomized to edaravone (n=69) or placebo (n=68). Mean age was 60 (range 20 to 75). Approximately 42% of patients were female. In both groups, mean disease duration was 1.1 years, mean baseline ALSFRS-R was 42, mean baseline FVC was 99% of predicted, and 91% of patients were using riluzole. Approximately one-fifth of patients in both groups presented with bulbar symptoms. The vast majority of patients (>97%) had sporadic disease. Dropouts were reasonably limited: 2/69 (3%) for edaravone and 8/68 (12%) for placebo.

On the 1° endpoint, there was a highly significant difference between treatment groups in favor of edaravone. At the end of Week 24, the ALSFRS-R score worsened by a mean (± standard deviation) of 4.4 ± 3.8 units in the edaravone group vs. 6.8 ± 4.9 in the placebo group. The least squares mean ± standard error of the difference between the groups and the 95% confidence interval of the mean was 2.49 ± 0.76 (0.99 to 3.98), p=0.0013, according to the applicant's last observation carried forward (LOCF) analysis.

The ALSFRS-R is plotted by treatment cycle in Figure 1, as adapted from the applicant's study report. Note that the end of cycle 6 occurred at Week 24.

Reference ID: 4094051

Figure 1: Study 19 – ALSFRS-R Score (mean ± SD) as a Function of Time



Dr. Massie conducted a number of alternative analyses on the 1° endpoint, including a mixed model repeated measures (MMRM) analysis (rather than the applicant's last observation carried forward analysis) and a Wilcoxon test of the joint rank of combined function and survival. (The latter analysis is generally recommended for ALS studies.) Per the MMRM analysis, the treatment effect was 2.83 ± 0.76, p=0.0003. Based on the Wilcoxon test, the p-value was 0.0009. An analysis of the treatment effect size by study site showed reasonable consistency among sites, i.e., the positive results were not driven by any site in particular. Using exploratory polynomial models, Dr. Massie found support for fairly consistent efficacy over most of the observed range of baseline ALSFRS-R scores.

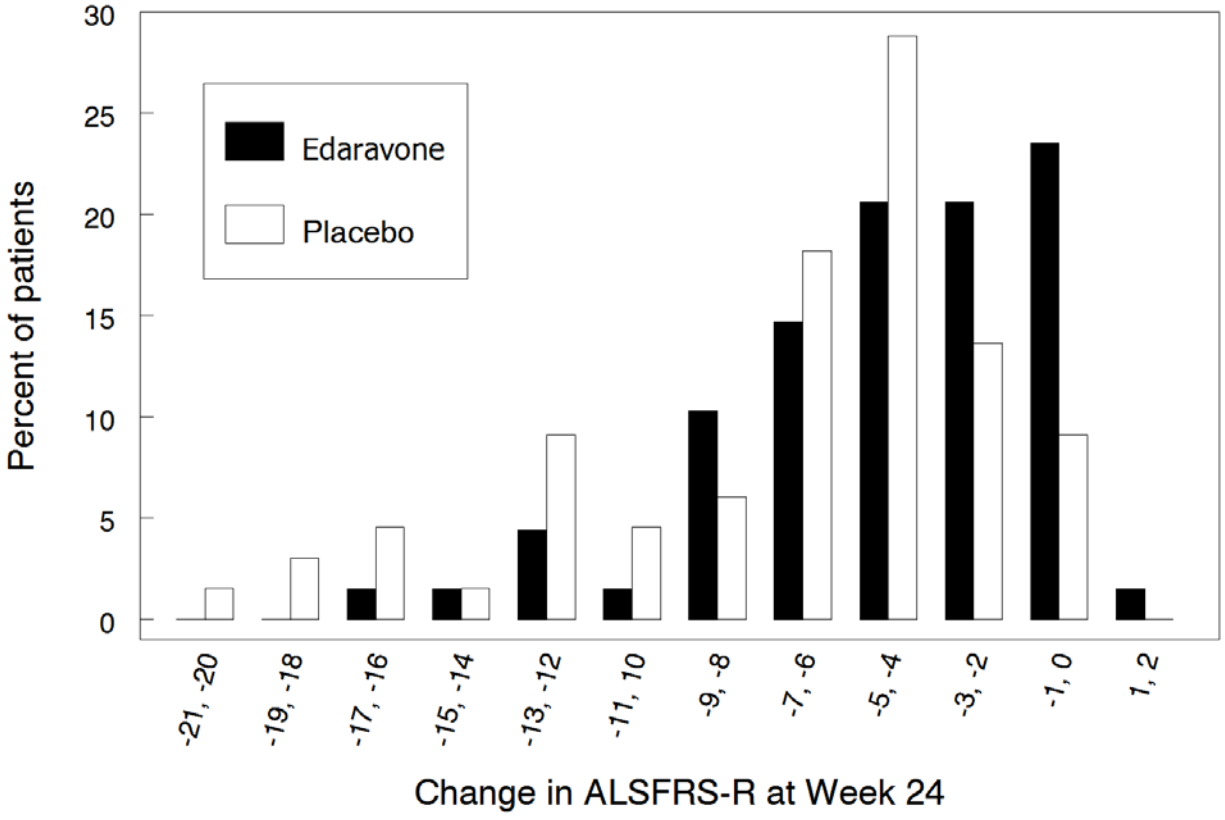
The treatment effect was fairly consistent across subgroups of sex, age, body mass index, disease duration, and El Escorial Revised Airlie House criteria (definite ALS; probable ALS), Table 1. Patients with better ALSFRS-R scores at baseline (categorized as those above the median score) tended to have a greater treatment effect (Table 1, bottom).

Table 1: Study 19 – Primary Endpoint, Subgroup Analyses by Baseline Demographics and Disease Characteristics (data compiled from \\cdsesub1\evsprod\NDA209176\0001\m5\datasets\mci186-19\analysis\legacy\datasets: adals.xpt and axsl.xpt)

			Δ ALSFRS-R		
Baseline variable	**number**	**% of population**	**Edaravone n=69**	**Placebo n=68**	**Delta**
All	137	100	-4.6	-7.0	**2.4**
Age (years)			mean	mean	
30 to 55	34	24.8	-3.3	-5.8	**2.5**
56 to 61	31	22.6	-5.4	-6.1	**0.8**
62 to 66	34	24.8	-5.0	-9.8	**4.8**
67 to 75	38	27.7	-4.4	-6.5	**2.1**
Sex					
Male	79	57.7	-4.4	-7.0	**2.6**
Female	58	42.3	-4.7	-6.9	**2.1**
Race					
Japanese	137	100	-4.6	-7.0	**2.4**
non-Japanese	0	0	-	-	**-**
Body mass index (BMI)					
15.6 to 19.1	20	14.6	-5.3	-5.9	**0.6**
19.2 to 21.5	48	35.0	-4.3	-8.4	**4.1**
21.6 to 23.4	34	24.8	-3.8	-6.3	**2.5**
23.5 to 38.1	35	25.5	-5.1	-6.1	**1.1**
Disease duration (years)					
0.2 to 1	72	52.6	-5.4	-7.8	**2.4**
1.1 to 2	65	47.4	-3.7	-6.0	**2.3**
Diagnostic criteria					
Definite ALS	55	40.1	-4.8	-6.3	**1.5**
Probable ALS	82	59.9	-4.4	-7.4	**3.0**
Baseline ALSFRS-R					
36 to 41	56	40.9	-6.4	-8.0	**1.6**
42 to 47	81	59.1	-3.4	-6.2	**2.8**

The distribution of change from baseline to Week 24 in ALSFRS-R scores shows a shift towards the right (less severity) in the edaravone group (Figure 2). More patients in the edaravone group experienced relative stability in ALSFRS-R scores (black bars, right), whereas more patients in the placebo group experienced meaningful declines in their ALSFRS-R (open bars, left).

Figure 2: Study 19 – Distribution of Changes in ALSFRS-R at Week 24 (data compiled from \\cdsesub1\evsprod\NDA209176\0001\m5\datasets\mci186-19\analysis\legacy\datasets\adals.xpt)



The ALSFRS-R is a multi-score instrument, in essence a composite endpoint that is the sum of 12 individual scores. It is worthwhile to explore how the individual components or domains of the ALSFRS-R contribute to efficacy (Table 2). Note that the scores for all 12 domains tend to worsen in both treatment groups, with respiratory function least affected. There is a fairly consistent treatment effect across the domains.

Table 2: Study 19 – Individual Components of the ALSFRS-R at Week 24 (data compiled from \\cdsesub1\evsprod\NDA209176\0001\m5\datasets\mci186-19\analysis\legacy\datasets\adals.xpt)

Parameter	Edaravone	Placebo	Delta
Speech	-0.3	-0.4	0.1
Salivation	-0.4	-0.5	0.1
Swallowing	-0.3	-0.6	0.3
Handwriting	-0.3	-0.3	0.1
Eating motion	-0.7	-1.0	0.4
Dressing and hygiene	-0.8	-1.0	0.2
Turning in bed and adjusting bed clothes	-0.5	-0.8	0.3
Walking	-0.4	-0.7	0.3
Climbing stairs	-0.6	-1.1	0.5
Respiration (1) Dyspnea	-0.2	-0.4	0.2
Respiration (2) Orthopnea	0.0	-0.1	0.1
Respiration (3) Respiratory insufficiency	0.0	0.0	0.0

As discussed above, there was no plan to address the Type-I error rate for the multiple 2° endpoints; therefore, they can be examined for nominal significance only (Table 3).

Table 3: Study 19 – Efficacy Results for 2° Endpoints

	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
%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	-0.75	-0.88	0.55

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

For the 2° endpoint time to death or certain disease progression, there were events in 2 patients in the edaravone group vs. 6 patients in the placebo group, but the log-rank *p*-value did not reach nominal statistical significance (Table 3). The FVC endpoint favored edaravone (-16%) slightly over

placebo (-20%), but did not reach nominal statistical significance. For the modified Norris scale,[3] there was a nominally significant difference between edaravone (-16) and placebo (-21), $p = 0.04$, according the applicant; $p = 0.052$ according to the statistical review when data from discontinuation visits were included.

For the patient-reported outcome ALSAQ40[4] score change, there was a nominally significant difference between the treatment groups favoring edaravone. There were no differences between the two groups in change of grip strength or pinch grip strength.

After completion of cycle 6 at Week 24, 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 patients on edaravone continued edaravone). Dr. Massie notes that the number of dropouts was substantial for the active extension phase, and somewhat different for the two original treatment groups: 24% for edaravone and 45% for placebo.

Dr. Massie undertook a joint rank analysis of survival and ALSFRS change based on a Wilcoxon test, using all events ranked from worst (death) to least impactful (loss of useful speech), followed by ranking patients with no events by their ALSFRS-R score (if non-missing). For this analysis, $p = 0.052$ for the difference at the end of Cycle 12.

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"), performed at the request of the Japanese Pharmaceutical and Medical Devices Agency (PMDA). Patients also received study drug for 6 cycles. There was no significant difference between treatment groups in change in ALSFRS-R score (-6.5 for edaravone; -6.0 for placebo, p = NS). The study was not powered to test the 1° hypothesis. With results numerically worse for edaravone, Dr. Bastings suggests the results are consistent with lack of efficacy in a more severely affected ALS population, but I am not convinced the data from such a small study are interpretable.

Comparability of the Japanese and US (Caucasian) Populations

Dr. Breder provides a detailed discussion of the information provided by the applicant in support of the generalizability of the effectiveness data to non-Japanese patients. His analysis includes a review of the comparability of ALS diagnoses, natural history, clinical practice parameters, and what is known regarding edaravone effectiveness and safety in non-ALS populations. The OCP review also finds that the pharmacokinetics of edaravone in Japanese and Caucasian subjects is comparable. I agree with

[3] 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 indicate better function.

[4] 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 appear problematic, as described in Dr. Breder's review. Higher scores are worse on this scale.

Reference ID: 4094051

these conclusions, as well as the views of Drs. Kozauer and Bastings, that the findings from Study 16 and 19 can be reasonably extrapolated to non-Japanese individuals with ALS.

Efficacy Conclusions

As discussed by Drs. Kozauer and Bastings and described in Guidance,[5] 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 an NDA. Moreover, and also as noted in the Guidance,[5] in some instances, FDA has relied on a single adequate and well controlled efficacy study with a low *p*-value to support approval, even without confirmatory evidence.

Dr. Kozauer provides a thoughtful analysis of the issues, highlighting two central questions:

1. whether the strength of Study 19 is adequate as a single study; and
2. whether the *post hoc* findings from Study 16 support the positive results of Study 19

Whether the Strength of Study 19 is Adequate as a Single Study

Dr. Breder concludes that Study 19 has many of the characteristics of a single adequate and well-controlled study that could make it adequate to support an effectiveness claim. He notes that this was a multi-center study that was robustly positive with a strong *p*-value, and points out that some of the 2° endpoints were supportive. Dr. Kozauer agrees with Dr. Breder's assessment of Study 19, adding that the 1° endpoint results are supported by a number of sensitivity analyses performed by Dr. Massie. Importantly, Dr. Kozauer adds that the 1° endpoint, ALSFRS-R, is a well-accepted and clinically relevant endpoint for clinical trials in ALS, and that the magnitude of the treatment effect is clinically meaningful (a 2.5-point difference favoring edaravone over a 24-week period). Dr. Kozauer also finds some support from the data from the open-label extension of Study 19, and highlights what he considers to be an important difference between treatment groups with respect to events of "certain disease progression," with 2 and 6 events in the edaravone and placebo groups, respectively. Dr. Bastings agrees that Study 19 could support approval as a single study, primarily based on the very persuasive results on the 1° endpoint, with some support provided by results of the 2° efficacy endpoints, albeit with their inherent weaknesses.

I will point out that Study 19 has additional characteristics that make it appropriate, as a single study, to provide evidence of effectiveness. In this multicenter study, no single site contributed an unusually large fraction of the patients, and no single site was disproportionately responsible for the treatment effect. In addition, despite the modest sample size, there was consistency across subsets of sex, age, body mass, initial symptoms (bulbar; limb), and El Escorial Revised Airlie House criteria (definite ALS; probable ALS). I also found that patients with better baseline ALSFRS-R scores (classified as above the median score) tended to have a greater treatment effect, a trend consistent with the applicant's hypothesis that the treatment effect is greater with less severe baseline disease. Finally, I will note that the *p*-values were quite strong: the *p*-value from the applicant's LOCF analysis was <0.0013, Dr. Massie's MMRM analysis found a *p*-value of 0.0003, and his Wilcoxon test of the joint rank of combined function

[5] FDA's Guidance for Industry, "Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products," May, 1998.

Reference ID: 4094051

and survival found a *p*-value of 0.0009. These results provide a level of assurance against a false positive result similar to what two studies, each at 0.05, would provide.

As noted in Guidance,[5] when considering whether to rely on a single trial, it is crucial to consider the possibility of an incorrect outcome, and examine all available data for their potential to either support or undercut reliance on the trial. Thus, although Dr. Massie finds the results on the 1° endpoint to be statistically positive (and positive on a number of alternative analyses he selected), he does not find Study 19 to be very persuasive in its own right because many of the 2° endpoints were not nominally statistically significant. The absence of a clearly positive 2° endpoint tends to undercut the overall persuasiveness of the study, although, as noted by many, the study was relatively small and there was no prospective plan to control the Type-1 error rate for the 2° endpoints. Nevertheless, one of the 2° endpoints (ALSAQ40 – a patient-reported outcome measure) was nominally statistically significantly positive, two (Modified Norris Scale and FVC) were close to being nominally statistically significant, and there was a favorable trend on time to death or certain disease progression. Drs. Breder, Kozauer, and Bastings appear to see these results as supportive, whereas Dr. Massie tends to view them negatively.

In summary, all agree that Study 19 was an adequate and well-controlled study, and that the study was positive. The study would be adequate to provide substantial evidence of effectiveness as a single study in the minds of some, whereas others would like to see confirmatory evidence.

Whether the *Post Hoc* Findings from Study 16 Support the Positive Results of Study 19

On the second question, i.e., whether the *post hoc* findings from Study 16 provide confirmatory evidence in support of Study 19, there are divergent views. Dr. Massie argues that Study 16 fails to provide confirmatory evidence of efficacy, noting the considerable weaknesses of the *post hoc* analyses, and what he considers to be circular reasoning. Dr. Breder believes that the data from Study 16 may be considered confirmatory. Dr. Kozauer believes that the question is a matter of judgement. He acknowledges reasons the applicant's *post hoc* subset analyses could be misleading, as argued by Dr. Massie, but points out that these results were used to generate a hypothesis that was subsequently confirmed by Study 19.

In light of the medical and societal context (a serious, fatal disease with a single approved treatment having modest benefit), Dr. Kozauer concludes that "…the strength of Study 19, combined with the supportive evidence from Study 16 along with the open-label extension data from Study 19, provide substantial evidence of the effectiveness of edaravone for the treatment of ALS."

Dr. Bastings believes that the statements and conclusions of both Dr. Massie and Dr. Kozauer have merit, but he agrees with Dr. Massie on this issue, and views the results of the *post hoc* analysis of Study 16 as primarily hypothesis generating.

The question of whether or not a study that *generates* a hypothesis (that is subsequently confirmed) actually provides *evidence* in favor of that hypothesis is a matter of judgment, and there is no guidance to help us in this matter. There is a natural tendency to doubt the strength of such evidence, particularly when there are significant limitations and weaknesses in the analyses used to develop the hypothesis in the first place. My opinion is that the data from Study 16 are supportive of the results of Study 19, but they are not "confirmatory" in the usual sense of the word.

Reference ID: 4094051

As discussed in Guidance,[5] whether to rely on a single adequate and well-controlled study is a matter of judgment. FDA has, in the past, construed a strongly positive single adequate and well-controlled trial to constitute substantial evidence of efficacy – even in the absence of confirmatory data – and we have based drug approvals on such evidence. The Guidance specifically refers to such reliance.

I agree with Dr. Bastings that considering the critical need for new treatments for ALS, it is appropriate to exercise a high level of flexibility in applying the effectiveness standard for a new drug. Given that ALS is an orphan disease, and in light of the study's modest size, I find it to be persuasive as a single study to provide substantial evidence of effectiveness. Factors in its favor include the clinical relevance of the 1° endpoint, the magnitude of the treatment effect, and the persuasiveness of the *p*-value. The *p*-value is particularly impressive given the modest size of the trial. Moreover, the results are robust to alternative statistical analyses, generally consistent across the 12 domains of the 1° endpoint, across study centers, and across important demographic and disease-related subgroups. Ideally, there would have been a statistically significantly positive 2° endpoint that could have supported efficacy, i.e., "multiple *studies* in a single study" as described in Guidance,[5] but this was not the case.

Our regulations (21 CFR 312.80) are intended to expedite the development, evaluation, and marketing of new therapies intended to treat persons with life-threatening and severely-debilitating illnesses, especially where no satisfactory alternative therapy exists: "…FDA has determined that it is appropriate to exercise the broadest flexibility in applying the statutory standards, while preserving appropriate guarantees for safety and effectiveness. These procedures reflect the recognition that physicians and patients are generally willing to accept greater risks or side effects from products that treat life-threatening and severely-debilitating illnesses, than they would accept from products that treat less serious illnesses." On the basis of the above, I agree with Dr. Bastings that Study 19 can support approval as a single study.

I also agree with the Division that the results of these studies, conducted in a Japanese population, can be generalized to the US population, for the reasons described in their reviews.

As noted by the Division, there is a concern that the treatment effect may be attenuated or absent in patients with more advanced ALS. As pointed out by Drs. Bastings and Kozauer, the subset of patients in Study 16 who were excluded from the *post hoc* analysis, i.e., those with more severe disease, trended worse on edaravone than on placebo. Moreover, the results of Study 18, an exploratory study conducted in patients with more advanced disease, also tended to be worse for edaravone than placebo. As explained by Dr. Bastings, although these findings do not establish that edaravone is deleterious in patients with more advanced ALS, they do raise concerns that edaravone's efficacy decreases as disease severity increases. I agree with Drs. Kozauer and Bastings, however, that ALS is heterogeneous, and that it would be counterproductive to limit the indication to patients with disease severity below a particular threshold. It is not known whether there is a specific stage of disease beyond which the treatment effect wanes.

Dr. Bastings stresses that edaravone's development program was conducted without FDA consultation, and there were a number of deficiencies. There is virtually no information on dose-response. Certainly we wonder whether the efficacy has been maximized (there is no evidence that this is the case), and there is little evidence of drug-related toxicity. Thus, it seems crucial to study more intensive dosing

Reference ID: 4094051

regimens. Dr. Bastings and I agree on this point, and we will seek a post-marketing commitment from the applicant to conduct a study to address this important issue.

8. Safety

I agree with the Division that the overall subject exposure is sufficient here. A total of 349 subjects received edaravone in the ALS development program: 306 for ≥ 6 months and 98 for ≥ 12 months. The Division concluded that the safety findings from the Japanese ALS subjects who were enrolled in the clinical trials are relevant to individuals with ALS in this country. Overall, 39% of subjects were female, mean disease duration was 1.3 years, some 19% initially had bulbar symptoms, and the vast majority of disease was sporadic.

As discussed by the Division, there were few deaths in the controlled portions of the ALS studies, with 4 and 2 deaths in the edaravone and placebo groups, respectively: 2.2% and 1.1%. These deaths were related to respiratory failure, which is the most common cause of death in ALS. As noted by Dr. Bastings, the small difference does not raise a safety concern, but is consistent with a lack of benefit of edaravone on survival (at least as detected in the course of a controlled study of 6 month's duration).

I found that the translation of the investigator's verbatim terms to preferred terms was inadequate, providing little confidence in the applicant's adverse event analyses (Table 4). For example, note that none of the 4 falls that occurred during the controlled portions of the trials were actually coded to the preferred term of "fall." (Thus, the applicant reported no falls during the controlled trials.) An adverse event with the verbatim term of "syncope" was coded to the preferred term "dizziness postural," when, in fact, the preferred term "syncope" exists. Thus, syncope was masked from the safety analysis.

I re-coded 70 (~7%) of the total 989 adverse events in the controlled periods of Studies 16, 18, and 19, as shown in Table 4 (in many cases there were multiple adverse events for a verbatim term).

Reference ID: 4094051

Table 4: Translation of Investigator's Verbatim Terms to Preferred Terms

Verbatim term	Applicant's Preferred Term	Action	My New/Added Preferred Terms
Abdominal pain after gastrostomy	Catheter site pain	recode	abdominal pain
Abdominal pain, loss of appetite	Abdominal pain	add	anorexia
Acute low back pain	Myofascial pain syndrome	recode	back pain
Contusion, injury (by fall) (right elbow, fingers, left calf)	Injury	add	fall; contusion
Dysesthesia in lower limbs	Limb discomfort	recode	dysaesthesia
Fall due to muscular weakness in lower limbs	Muscular weakness	add	fall
Fascial lower back pain	Myofascial pain syndrome	recode	back pain
Insect bite	Arthropod sting	recode	arthropod bite
Left eyelid hemorrhage	Periorbital contusion	recode	haemorrhage
Left glutealis contusion due to fall	Contusion	add	fall
Lightheadedness	Feeling abnormal	recode	dizziness
Lower limb dysfunction	Musculoskeletal disorder	recode	muscular weakness
Neuralgiform pain	Pain	recode	neuropathy
Right arm rash	Dermatitis contact	recode	rash
Right glutealis contusion due to fall	Contusion	add	fall
Right hand flush and swelling	Arthropod sting	recode	local swelling
Seborrheic eczema	Seborrhoeic dermatitis	recode	eczema
Sensory dysfunction of feet	Sensory disturbance	recode	neuropathy
Syncope	Dizziness postural	recode	syncope
Worsening of ALS (disability of ambulation)	Abasia	add	muscular weakness
Worsening of ALS (disability of independent ambulation)	Gait disturbance	add	muscular weakness
Worsening of ALS (lack of upper limb function)	Musculoskeletal disorder	recode	muscular weakness
Worsening of ALS (loss of upper limb function)	Musculoskeletal disorder	recode	muscular weakness
Worsening of ALS (lower limb dysfunction)	Gait disturbance	recode	muscular weakness
Worsening of ALS (upper limb function disorder)	Musculoskeletal disorder	recode	muscular weakness

After re-coding the adverse events for the placebo-controlled periods of Studies 16, 18, and 19 and grouping similar/related terms, I found no important differences in frequencies of serious adverse events. This is consistent with the results of the Division's review.

The overall adverse events in placebo-controlled studies are summarized in Table 5 (serious and non-serious together). The adverse events at the top of the table will be tabulated in Section 6 of labeling (Adverse Reactions).

Table 5: Adverse Events in the Placebo-Controlled Periods of Studies 16, 18, and 19

	edaravone n=184	placebo n=184	RR
Pertinent positives			
Contusion	27 (15%)	16 (9%)	1.7
Gait disturbance	23 (13%)	17 (9%)	1.4
Headache	18 (10%)	11 (6%)	1.6
Dermatitis	14 (8%)	9 (5%)	1.6
Eczema	12 (7%)	8 (4%)	1.5
Respiratory failure, respiratory disorder, hypoxia	11 (6%)	7 (4%)	1.6
Glycosuria	7 (4%)	3 (2%)	2.3
Tinea infection	7 (4%)	4 (2%)	1.8
Pertinent negatives			
Muscular weakness, malaise	31 (17%)	30 (16%)	1.0
Dysphagia	18 (10%)	21 (11%)	0.9
Rash	7 (4%)	8 (4%)	0.9
Transaminase elevation	5 (3%)	8 (4%)	0.6
Neuralgia, neuritis, neuropathy	2 (1%)	4 (2%)	0.5
Fall	2 (1%)	1 (1%)	2.0
Allergic reaction, hypersensitivity	2 (1%)	3 (2%)	0.7
Bleeding	1 (1%)	10 (5%)	0.1
Fracture	1 (1%)	7 (4%)	0.1
Injection site reaction	1 (1%)	4 (2%)	0.3

I find it difficult, however, to attribute the above differences to a drug effect, lacking a range of exposures that would be needed to assess a dose-response, and lacking a reasonable mechanism of action to support them. Interpretation is difficult in light of the multiplicity. One needs only to look at bleeding (with 10 events in the placebo group and 1 in the drug group) and fractures (7 events vs. 1) to understand how bizarre findings can arise from play-of-chance. Some of the negatives in the table are pertinent: despite a large number of adverse events of muscular weakness and dysphagia (manifestations of ALS), there is no difference between groups. Although the numbers of events are too small to be very informative, there are no differences in neuropathy (a concern based on non-clinical data), rash, or allergic reactions.

The Division noted the higher incidence of skin-related adverse events in edaravone-treated patients compared to placebo, including eczema (7% vs. 2%), dermatitis contact (6% vs. 3%), rash (4% vs.2%), and erythema (3% vs. 2%). Having found some additional cases of rash (4% in both groups), the difference

Reference ID: 4094051

seems less impressive. As noted, there was also a case of toxic skin eruption in the edaravone group, with few details.

The Division found no important differences in laboratory measurements or vital signs assessments between the edaravone and placebo groups.

The postmarketing data from Asia in patients treated for ALS, acute ischemic stroke, and subarachnoid hemorrhage provided a number of reports of cases, but these were confounded or otherwise deficient in detail to make reasonable assessments of causality. Hypersensitivity/ anaphylaxis was a possible exception, as 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 Section 5 (Warnings and Precautions) of the labeling, and with the concurrence of the Division, I agree.

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 agree with the Division that a Medication Guide is not justified on the basis of the safety profile of the drug.

Dr. Bastings notes that the applicant has not yet conducted a thorough QT (TQT) study. The limited ECG data submitted by the applicant did not identify a signal of QT prolongation. I agree with the Division that, considering the unmet medical need of patients with ALS, a TQT study can be deferred to the postmarketing period, and will 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, the clinical trial design is acceptable, and the endpoint was not novel.

10. Pediatrics

Not applicable; 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 review concludes that edaravone does not have abuse potential, and recommends eliminating Section 9 (Abuse and Dependence) from labeling. The Division and I concur with this plan.

Reference ID: 4094051

12. Labeling

All labeling issues have been resolved with the applicant. As discussed by Dr. Kozauer, the applicant proposed warnings and precautions [redacted] (b) (4), but these were deleted as there was no medical justification for these warnings.

13. Postmarketing Recommendations

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 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 agree with the Division in including a postmarketing commitment to assess the safety and efficacy of higher doses of edaravone. There is no evidence upon which to base a conclusion that the drug's benefit has been maximized at the labeled dose, and there is no obvious dose-related toxicity. Higher doses should be studied with the hope of improving efficacy. Also, as noted by Dr. Bastings, identification of a more rational dosing regimen (i.e., daily or near daily) would be helpful.

Reference ID: 4094051

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ELLIS F UNGER
05/04/2017