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APPLICATION NUMBER:

209176Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	May 2, 2017
From	Nick Kozauer, MD
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	NDA 209176
Applicant	Mitsubishi Tanabe Pharma Group
Date of Submission	June 16, 2016
PDUFA Goal Date	June 6, 2017
Proprietary Name / Non-Proprietary Name	Radicava (edaravone)
Dosage form(s) / Strength(s)	Intravenous injection, 60mg (30mg/100mL)
Applicant Proposed Indication(s)/Population(s)	Amyotrophic lateral sclerosis (ALS)
Recommendation on Regulatory Action	Approval

1.   Benefit-Risk Assessment

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Benefit-Risk Summary and Assessment

Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disease that results in degeneration of both upper and lower motor neurons. The pattern of neurologic signs and symptoms that an individual patient can experience can vary based on the nerves that are involved. However, the disease condition generally progresses rapidly and increasing muscle weakness leads to profound impairments in patient's functional abilities. The majority of patients die within 2-4 years after diagnosis from respiratory muscle involvement, with approximately 20% surviving to between 5-10 years from symptoms onset. The cause of ALS has not been established.

Edaravone is thought to be a free radical scavenger that the applicant proposes counters oxidative damage that is hypothesized to occur in the nervous system of ALS patients. Riluzole, approved in 1995, is the only FDA-approved treatment for ALS. The clinical trials that led to that approval demonstrated a modest (2-3 month) increase in survival, with no clear benefit on measures of muscle strength or daily function.

The effectiveness of edaravone was primarily established based on the results of a 24-week, double-blind, placebo-controlled trial in subjects with ALS (Study 19). The population from Study 19 was defined to have relatively less severe disease based on standard diagnostic criteria, clinical evaluations (e.g., ALS rating scale score and percent-forced vital capacity [%FVC] results), and time since diagnosis at Screening. 206 subjects were enrolled and randomized equally to receive either edaravone 60mg administered intravenously (Cycle 1 involved receiving 14 days of treatment followed by 14 days off, with subsequent cycles alternating between treatment on 10 out of 14 days followed by 14 days off). The trial demonstrated a highly statistically significant and clinically meaningful difference of 2.5 points less decline on the 48 point ALS Functional Rating Scale – Revised (ALSFRS-R) at Week 24 (p=0.0013). This finding was confirmed by a variety of sensitivity analyses. Although not statistically controlled for Type I error, the analyses of a number of the trial's secondary endpoints also were consistent with the established effect on the primary endpoint.

The results from Study 19 were supported by the findings from Study 16, which was sequentially conducted first. Study 16 had a similar design to Study 19, but employed a more broadly defined set of enrollment criteria. The trial failed to demonstrate a statistically significant effect on its primary endpoint of the ALSFRS-R at Week 24. However, post hoc analyses conducted by the applicant suggested that there was an efficacy signal in a more narrowly defined patient population (i.e., as defined above for Study 19). This hypothesis was subsequently tested and confirmed in Study 19, as discussed. In this context, when viewed together, the post hoc results from Study 16 are able to lend confirmatory support to the positive findings from Study 19.

There are no significant safety signals of concern with edaravone. There were no apparent imbalances between edaravone-treated subjects and placebo-treated subjects 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 the edaravone-treated subjects and placebo. The non-United States (US) postmarketing safety database from the acute ischemic stroke (AIS) and subarachnoid hemorrhage (SAH) populations was largely confounded by the underlying diseases but suggested a possible association of events of hypersensitivity/anaphylaxis with edaravone treatment.

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• ALS is a fatal neurodegenerative disease that selectively attacks both upper and lower motor neurons. Patients are typically diagnosed between 40-70 years of age and experience progressive muscle weakness and atrophy, with death typically 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 typically within 2-4 years of diagnosis.
Current Treatment Options	• Riluzole, approved in 1995, is the only FDA-approved treatment for ALS. The clinical trials leading to that approval demonstrated a modest (2-3 month) increase in survival without any clear benefit on measures of muscle strength or daily function.	There is a clear need for more effective therapies for the treatment of ALS.
Benefit	• The effectiveness of edaravone was primarily established based on the results of a 24-week, double-blind, placebo-controlled trial in subjects with ALS (Study 19). The population from Study 19 was defined to have relatively less severe disease based on standard diagnostic criteria, clinical evaluations (e.g., ALS rating scale score and percent-forced vital capacity [%FVC] results), and time since diagnosis at Screening. 206 subjects were enrolled and randomized equally to receive either edaravone 60mg administered intravenously (Cycle 1 involved receiving 14 days of treatment followed by 14 days off, with subsequent cycles alternating between treatment on 10 out of 14 days followed by 14 days off). The trial demonstrated a highly statistically significant and clinically meaningful 2.5 points less decline on the 48 point ALS Functional Rating Scale – Revised (ALSFRS-R) at Week 24 (p=0.0013). This finding was confirmed by a variety of sensitivity analyses. Although not statistically controlled for Type I error, the analyses of a number of the trial's secondary endpoints also were consistent with the established effect on the primary endpoint. • The results from Study 19 were supported by the findings from Study 16, which was sequentially conducted first. Study 16 had a similar design to Study 19, but employed a more broadly defined set of enrollment criteria. The trial failed to demonstrate a statistically significant effect on its primary endpoint of the ALSFRS-R at Week 24. However, post hoc analyses conducted by the applicant suggested that there was an efficacy signal in a	This application has established that edaravone is effective for the treatment of patients with ALS.

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
	more narrowly defined patient population (i.e., as defined above for Study 19). This hypothesis was subsequently tested and confirmed in Study 19, as discussed. In this context, when viewed together, the post hoc results from Study 16 are able to lend confirmatory support to the positive findings from Study 19.	
Risk	• There are no significant safety signals of concern with edaravone. There were no apparent imbalances between edaravone-treated subjects and placebo-treated subjects 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 the edaravone-treated subjects and placebo. The non-United States (US) postmarketing safety database from the acute ischemic stroke (AIS) and subarachnoid hemorrhage (SAH) populations was largely confounded by the underlying diseases but suggested a possible association of events of hypersensitivity/anaphylaxis with edaravone treatment.	The safety profile of edaravone is acceptable and supports an approval action for this application.
Risk Management	• There are no safety signals of concern that would warrant any addition risk management beyond clear product labeling that conveys the known safety profile of edaravone.	Risk management can be achieved through clear product labeling and routine postmarketing surveillance.

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2.   Background

This application contains data in support of the efficacy of edaravone (MCI186), administered intravenously (IV), for the treatment of amyotrophic lateral sclerosis (ALS). Edaravone is a new molecular entity (NME) and has not been approved in the United States (US) for any indication and has not previously been the subject of any marketing application. Edaravone has been marketed for many years in Japan and in other Asian countries for the short-term treatment of acute ischemic stroke (AIS) (b) (4) More recently, edaravone was approved in Japan for the treatment of ALS in June 2015, and in South Korea in December 2015.

Riluzole, approved in 1995, is the only FDA-approved treatment for ALS. The clinical trials that led to that approval demonstrated a modest (2-3 month) increase in survival, with no clear benefit on other measures of muscle strength or daily function.

ALS (also referred to as Lou Gehrig's disease) is a fatal neurodegenerative disease that selectively attacks both upper and lower motor neurons. Patients are most commonly diagnosed between 40-70 years of age and experience progressive muscle weakness and atrophy which ultimately lead to the loss of the ability to initiate and control voluntary movement. Death usually results from respiratory muscle involvement. Most patients die within 2-4 years after the diagnosis, although approximately 20% survive to between 5-10 years from symptom onset.

Edaravone is thought to be a free radical scavenger that the applicant proposes counters oxidative damage that is hypothesized to occur in the nervous system of ALS patients.

The applicant has provided data from a randomized, double-blind, 6-month, placebo-controlled trial that is intended to serve as the basis for the conclusion that edaravone is effective for the treatment of ALS (Study MCI186-19 [19]). Additional supportive efficacy data is provided from a similarly designed trial (Study MCI186-16 [16]) that was conducted prior to Study 19. Although the results of the overall findings from Study 16 were not statistically significant, the applicant conducted a post hoc analysis in a more restricted patient subgroup that suggested a potential treatment benefit and informed the design of Study 19.

The regulatory history for edaravone is detailed in Dr. Christopher Breder's clinical review and the reader is referred there for additional information.

3.   Product Quality

The technical lead on the Office of Product Quality (OPQ) review was Dr. Wendy Wilson (Dr. Wilson's review lists the entire OPQ team that was involved with the review of this application). The OPQ review indicates that all product quality review issues have been adequately addressed and any potential related risks to patient safety, product efficacy, and product quality have been appropriately mitigated. Therefore, OPQ concludes that an approval action can be taken for this application and recommends a (b) (4) re-test period for the drug substance and a 36-month drug product commercial expiration period when stored at a controlled room temperature in the intended commercial packaging.

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4. Nonclinical Pharmacology/Toxicology

The nonclinical reviewer for this application is Dr. David Carbone, with Dr. Lois Freed perfroming a secondary review. Dr. Carbone concludes that this application is approvable from a pharmacology/toxicology perspective. The following are among the key conclusions from the nonclinical reviews:

- In the safety pharmacology studies, increases in lacrimation and ptosis, and decreases in spontaneous movement in male mice and rats following a single IV dose of 30 or 100 mg/kg of edaravone. Decreases in body temperature were observed in male mice administered a single 100 mg/kg IV dose of edaravone. In mongel dogs, single IV doses of 30 or 100 mg/kg of edaravone resulted in transient decreases in blood pressure and increases in carotid blood flow and heart rate.

- The toxicity of edaravone was evaluated by IV bolus or continuous infusion in Wistar rats, beagle dogs, and cynomolgus monkeys (continuous infusion only). Primary toxicities following IV bolus or short (i.e., less than 4 hour) infusion in male and female rats and dogs included transient CNS signs (e.g., sedation and hypoactivity) and decreases in weight gain at doses greater than 10 or 30 mg/kg, respectively. Continuous infusion in male and female rats and dogs was associated with hematologic signs of regenerative anemia at doses greater than 300 and 30 mg/kg, respectively.

- Continuous infusion in dogs and monkeys also resulted in peripheral nerve degeneration. Additional studies in dogs indicated that nerve fiber degeneration was typically restricted to the axons and was accompanied by digestion chambers. These data suggest that the nerve fiber degeneration induced by edaravone may be reversible, although complete recovery was not observed after recovery periods up to 13 weeks. A mechanism explaining edaravone-induced nerve fiber degeneration was never defined, but additional studies suggest a role for vitamin B6 deficiency.

- Renal toxicity was not seen in the toxicology studies, although there is some suggestion from mechanistic studies in rats that edaravone may increase renal exposure to cephalosporin antibiotics.

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

- Edaravone was negative in a complete battery of *in vitro* and *in vivo* genetic toxicology studies. Carcinogenicity studies of edaravone administered in diet, conducted by the National Cancer Institute in 1979, were referenced by the applicant. There were no indicators of carcinogenicity, but issues including high mortality in a vehicle group and

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inconsistent dosing reduce the confidence in these studies. Adequately conducted carcinogenicity studies should be conducted post-marketing.

5. Clinical Pharmacology

An integrated Office of Clinical Pharmacology (OCP) review was written by Dr. Xinning Yang (the primary reviewer), Dr. Atul Bhattaram, Dr. Kevin Krudys, and Dr. Sreedharan Sabarinath (the clinical pharmacology team lead).

The following are among the key conclusions of the OCP review:

- The population pharmacokinetic (popPK) analyses that were conducted by the applicant to demonstrate the PK similarities between Japanese and Caucasian ALS patients support the conclusion that these groups were similar in this respect. This determination is particularly important, as the clinical effectiveness trials that have been provided with this application were conducted exclusively in Japanese subjects with ALS.

- No dose individualization is recommended based on intrinsic or extrinsic factors.

- 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 concludes that the applicant's proposed dosing regimen can be used in patients with mild and moderate hepatic impairment with careful adverse event (AE) monitoring. However, no dosing recommendations can be made in patients with severe hepatic impairment until a study is conducted to assess PK in that population. OCP recommends that such a study be conducted as a postmarketing requirement should an approval action be taken.

- The 60mL volume difference between the infusion solution used in the Phase 3 clinical trials (a 30mg/20mL ampule was diluted to 140mL with saline) and the to-be-marketed product (which will be supplied in a bag, as opposed to an ampule, administered as 200mL solution in saline) was not considered to be significant.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical- Efficacy

Dr. Christopher Breder was the clinical reviewer for this application. Dr. Tristan Massie was the biometrics reviewer, and Dr. Kun Jin was the biometrics team lead for this application.

The following table, copied from Dr. Massie's review, summarizes the clinical effectiveness trials that have been submitted in support of the current application:

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Table 1 Phase 3 Efficacy Studies of Edaravone in ALS

Trial ID	Design*	Treatment/ Sample Size	Endpoint/Analysis	Preliminary Findings
19	DB (24 wks)	Drug / 69 Placebo/ 68	Primary: ALSFRS-R Change at 24 Weeks	P=0.0013 (0.0037)*
16	DB (24 wks)	Drug /100 (39)# Placebo/99 (29)#	Primary:ALSFRS-R Change at 24 Weeks	Overall: p=0.4108 Post-hoc subgroup# p=0.017 (.0147)

* MC: multi-center, R: randomized, DB: double-blind, PG: parallel group, PC: placebo controlled, AC: active controlled
24 week active extension
#Post hoc subgroup

The main support for this application comes from the results of Study 19. Importantly, Study 16 was conducted first, but failed to demonstrate an effect on its prespecified primary endpoint. However, a post hoc subgroup analysis conducted by the applicant suggested a treatment effect in a more narrowly defined subgroup of patients with somewhat less severe disease, which subsequently informed the design of Study 19. These trials will be discussed sequentially, below. Both trials enrolled only Japanese subjects with ALS.

Also of note, the applicant provided the results of a small (n=25) 24-week trial conducted in Japanese subjects with advanced ALS that was performed in response to a requirement made by Japanese regulatory authorities (the PMDA). This trial was negative, but was also too small to be considered anything but exploratory and therefore is not a significant consideration in the review of the current application.

Study 16
Study 16 was a placebo-controlled, double-blind, parallel-group trial conducted in 206 Japanese subjects with ALS. As discussed in detail in Dr. Breder's review, these subjects were considered to have somewhat less severe disease (based on Japanese staging criteria, forced vital capacity [FVC] values greater than 70% of predicted, and a diagnosis within 3 years of Screening). Subjects were randomized in a 1:1 ratio to receive either edaravone or placebo. The following graphic, copied from Dr. Massie's review, depicts the design of the trial:

Figure 1 Study 16: Outline of Study Design
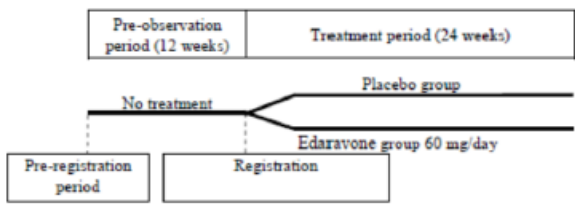
The trial consisted of the following 2 main phases:

- Pre-observation period: a 12-week period before the start of treatment (designed to identify subjects who demonstrated between a 1 to 4 point decline on the ALSFRS-R [a 48-point scale] during this period to continue on to the treatment period). The goal of this period was to identify subjects who were more likely to decline during the double-blind treatment period.
- Treatment: a 24-week double-blind treatment period.

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Treatment was administered as follows:

- Cycle 1: a 60mg IV dose of edaravone administered daily for 14 days, followed by a 14 day drug-free period
- Cycles 2-6: a 60mg IV dose of edaravone administered for 10 days during a 14-day period, followed by a subsequent 14-day drug-free period (with the cycle repeating 5 times through Week 24)

The primary efficacy endpoint was based on the change from Baseline on ALSFRS-R scores to the end of Cycle 6 of treatment (i.e., Week 24), using an analysis of covariance (ANCOVA) with the last observation carried forward (LOCF). The ALSFRS-R is an accepted functional scale for use in ALS trials. The scale consists of 12 functional domains that are rated from 0-4 leading to a maximum score of 48, with lower scores indicating greater decline. Please refer to Dr. Breder's review for a more detailed description of the measure. The results in the overall population numerically favored treatment but were not statistically significant (LS Mean change from Baseline of -6.35 ± 0.84 in placebo group versus -5.70 ± 0.85 in the edaravone group; p=0.41).

Following the results of the pre-specified primary endpoint analysis, the applicant conducted additional post hoc subgroup analyses in what was defined as the Efficacy Expected Subpopulation (EESP) consisting of subjects with less severe disease who had all 12 ALSFRS-R subdomain scores that were all greater than 2 at the beginning of Cycle 1 and who had an FVC of greater than 80% at the beginning of Cycle 1. The applicant then further refined the population to only include subjects who met the EESP criteria, had "definite" or "probable" ALS diagnoses based on the commonly accepted El Escorial Revised Airlie House criteria, and who had been diagnosed within 2 years of Screening (Definite/Probable/EESP/2Y).

The following table, copied from Dr. Massie's review, presents the results of the applicant's post hoc subgroup analyses, along with the results of the complimentary post hoc analyses in subjects who did not meet these revised criteria:

Table 2 Difference in ALSFRS-R between Baseline in Cycle 1 and the End of Cycle 6 (LOCF) for Study MCI186-16 (FAS, EESP, Definite or Probable/EESP/2y)

Study number (Population)	Group	Number of subjects in LOCF analyses	Adjusted mean LS mean±SE	Between-group differences in the adjusted mean LS mean±SE (95% CI)	p-value
MCI186-16 (FAS)	P group	99	-6.35±0.84	0.65±0.78 (-0.90 , 2.19)	p=0.4108
	E group	100	-5.70±0.85		
MCI186-16 (EESP)[a]	P group	46	-7.06±1.13	2.20±1.03 (0.15 , 4.26)	p=0.0360
	E group	53	-4.85±1.24		
MCI186-16 (definite or probable/EESP/2y)[a]	P group	29	-7.59±1.34	3.01±1.33 (0.35 , 5.67)	p=0.0270
	E group	39	-4.58±1.55		
MCI186-16 (non-EESP)[a]	P group	53	-5.24±1.25	-1.42±1.16 (-3.73 , 0.89)	p=0.2251
	E group	47	-6.65±1.17		
MCI186-16 (non-"definite or probable/EESP/2y")[a]	P group	70	-5.54±1.08	-0.57±1.00 (-2.55 , 1.41)	p=0.5711
	E group	61	-6.11±1.03		

Note: LOCF was applied to subjects who completed Cycle 3 (subjects who reached 81 days after treatment initiation). Subjects who dropped out before Day 81 were excluded.
[a] EESP, Definite or Probable/EESP/2y, non-EESP, and non-"Definite or Probable EESP/2y" analyses were post-hoc.

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The applicant believed that these results suggested the possibility that edaravone might be most effective in ALS patients with less severe disease, which led to the conduct of Study 19.

Dr. Massie's statistical review questions the applicant's conclusions based on these nominally significant post hoc findings for a number of reasons. Most importantly, these analyses were not prespecified, and the the prespecified primary endpoint analysis in the overall population was not significant. Dr. Massie further describes an exploratory analysis that he conducted which suggests that within the less severe post hoc subgroups, the treatment effect seemed to be paradoxically larger in the subjects with worse baseline ALSFRS-R scores. He argues that this finding is inconsistent with what would be expected if edaravone was actually most effective in earlier stage disease. Dr. Massie further discusses baseline imbalances in the revised subgroups, such as the fact that 21.9% of placebo subjects were not treated with riluzole, as compared to only 7.5% of edaravone subjects in the Definite/Probable/EESP/2Y population. In addition, Dr. Massie's review describes inconsistent results on a number of other exploratory tests of treatment interactions.

Dr. Massie concludes that the baseline imbalances between the post hoc treatment groups and his additional finding of non-normality of the ALSFRS-R distribution are reasons to question the interpretability of the applicant's results. Dr. Breder largely agrees with Dr. Massie's conclusions, but believes that the findings can still play a contributory role to the overall evidence of effectiveness of edaravone for the treatment of ALS.

Although they can only be viewed as exploratory, Dr. Breder's review also discusses a number of nominally significant results for the secondary endpoints from the applicant's post hoc subgroup analyses in the EESP and Definite/Probable/EESP/2Y populations. Many of these simply represent different aspects of the ALSFRS-R, so it is not surprising that these would also reach nominal significance. However, Dr. Breder notes that the change from Baseline in %FVC and the Limb Norris Scale also seem to favor edaravone in these subgroups. There was no survival benefit (or trend towards worse survival) across any of these populations as there were only 2 deaths in both the drug and placebo groups in the overall population through Week 24.

Study 19
Study 19 was a placebo-controlled, double-blind, parallel-group trial that enrolled 137 Japanese subjects with ALS. The population was defined according to the Definite/Probable/EESP/2Y criteria, based on the applicant's post hoc subgroup analysis of Study 16. Subjects were randomized in a 1:1 ratio to receive either edaravone or placebo. The trial had a similar design to Study 16 involving a 12-week pre-observation period and a 24-week treatment period consisting of Cycles 1-6. Study 19 also offered an additional 24-week open-label extension period (Cycles 7-12). Dosing was identical to Study 16. Similarly, the primary efficacy endpoint was the change from Baseline to the end of Cycle 6 in ALSFRS-R scores analyzed using ANCOVA with LOCF.

The result of the applicant's analysis of the primary endpoint was highly statistically significant (LS Mean change from Baseline in ALSFRS-R scores of -7.50±0.66 for placebo versus -5.01±0.64 for edaravone; p=0.0013). Dr. Massie presents similar highly significant results of a mixed-model repeated measures (MMRM) analysis of the primary endpoint as a treatment difference favoring edaravone of 2.83±0.76 (p=0.0003), noting that dropouts were very low in the 24-week treatment period (2/69 [3%] for edaravone versus 8/68 [12%] for placebo). Dr. Massie also presents results of a Wilcoxian test of the joint rank of combined function and survival which favored edaravone

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(p=0.0009). Dr. Massie's review explores a number of additional analyses based on various normality assumptions for the ALSFRS-R score distributions, all of which support the primary analysis results. Dr. Breder's review similarly presents a number of related sensitivity analyses which are also consistent with the primary analysis results.

Unfortunately, there was no statistical control for Type I error in the applicant's analysis of any of the trial's secondary endpoints. As mortality is an important consideration in ALS trials, the applicant analyzed the time to death or certain disease progression, the latter of which was defined as reaching certain key milestones (e.g., tracheostomy, tube feeding, etc.). There were no deaths and 2 progression events in the treatment group as compared to no deaths and 6 progression events in the placebo group in the 24-week treatment period (these difference failed to reach nominal significance; p=0.13[log-rank test]). In a similar analysis that also included the 24-week OLE period, (subjects were characterized as either receiving edaravone in both periods [E-E] or placebo in the treatment period followed be edaravone in the OLE [P-E]) there were 19 events in the P-E group versus 10 in the E-E group (p=0.07). In the OLE analysis, there were 2 deaths in the P-E group as compared to 1 death in the E-E group.

The following table, copied from the application, summarizes the results on the secondary endpoints from Study 019:

Table 2.7.3-19: Analysis of Other Secondary Endpoints of Change from Baseline in Cycle 1 to the End of Cycle 6 (LOCF) (Study MCI186-19 Double-blind, FAS)

Endpoints	Group	Number of subjects	Adjusted mean change from Baseline LS mean ± SE	Adjusted mean change from Baseline LS mean ± SE (95% CI)	p-value
ALSAQ40 score	P group	64	26.04 ± 3.53	-8.79 ± 4.03 (-16.76, -0.82)	p=0.0309
	E group	68	17.25 ± 3.39		
Modified Norris Scale score (Total)	P group	63	-20.80±2.06	4.89±2.35 (0.24, 9.54)	p=0.0393
	E group	68	-15.91±1.97		
Grip strength	P group	66	-4.19±0.56	0.11±0.64 (-1.15, 1.38)	p=0.8583
	E group	68	-4.08±0.54		
Pinch grip strength	P group	66	-0.88±0.14	0.10±0.16 (-0.23, 0.42)	p=0.5478
	E group	68	-0.78±0.14		

LOCF was applied to the subjects who completed Cycle 3 (subjects who reached 81 days after treatment initiation). Subjects who dropped out before Day 81 were excluded. Source: MCI186-19 CSR Table 11.4.1.1-31, 33, 35, 37, and 38.

Dr. Massie's review agrees with the applicant's results of these analyses. Dr. Breder's review also graphically presents (using a stacked bar graph) a descriptive analysis of the changes in the Japanese ALS severity classification (FAS) scores which appears to indicate that the placebo group had a greater proportion of subjects showing increased disability.

Efficacy Conclusions

- *Demonstration of Effectiveness*

  The 1998 FDA Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products describes scenarios where evidence from a single clinical study can fulfil the criteria for providing substantial evidence for effectiveness under 21 CFR 314.126. Specifically, the Guidance refers to section 115(a) of the FDA Modernization Act (1988) which makes clear that the Agency may consider "data from one adequate and well-controlled clinical

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investigation and confirmatory evidence" to constitute substantial evidence of effectiveness in support of an approval of a marketing application.

The central questions that need to be considered in determining whether such evidence has been provided in this application relate to:

- The strength of the results from Study 19, and;
- The ability of the post hoc findings from Study 16 to support the positive results of Study 19.

With respect to the first consideration, Study 19 had a highly statistically significant effect (p=0.0013) on the ALSFRS-R, which is an accepted endpoint for clinical trials in ALS. This result was also supported by highly positive results on a number of various sensitivity analyses. In addition, the roughly 2.5-point treatment difference favoring edaravone over only a 24-week period is clinically meaningful. Although unfortunately not statistically controlled for Type I error, the overall pattern of results on the analyses of the trial's secondary endpoints also favored edaravone, including an important difference of 6 events of "certain disease progression" in placebo as compared to 2 such events in the edaravone-treated subjects. Based on these observations, I agree with Dr. Breder's conclusion that Study 19 provides strong evidence in support of the effectiveness of edaravone for the treatment of ALS. This finding is supported by the analysis of the OLE data that indicate a total of 10 deaths/events of certain disease progression in the E-E group as compared to 19 in the P-E group.

Ultimately, there is little disagreement between the clinical and biometrics reviews with respect to the results of Study 16. Dr. Massie's review rightly points out a number of possible reasons that the post hoc subgroup analyses could be misleading (e.g., baseline imbalances). However, the fact remains that these results were correctly used to generate a hypothesis which was subsequently confirmed based on the results from Study 19. Therefore, 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.

Particularly in the context of a serious and fatal condition with only one approved treatment with limited benefit, it is my opinion that the strength of Study 19, combined with the supportive evidence from Study 16 along with the OLE data from Study 19, provide substantial evidence of the effectiveness of edaravone for the treatment of ALS.

- *Durability of Treatment*

Dr. Massie expresses some concern that well-controlled evidence regarding the durability of the treatment effect of edaravone beyond 24 weeks has not been provided. I agree. However, in the context of a disease that is frequently fatal within 2-4 years after onset, a minimum of a 6-month benefit on meaningful daily function is inherently clinically important on its own.

- *Indicated Population*

Both Dr. Massie and Breder agree that there is a question as to how effective edaravone is for the treatment of ALS patients who do not meet the applicant's revised enrollment criteria used for Study 19. In fact, as described above, Dr. Massie's review suggests that the post hoc

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analyses of the subgroups from Study 16 that did not meet the EESP and Definite/Probable/EESP2Y criteria did not come close to reaching nominal significance. Although the results of Study 16 raise some doubts regarding the ability of edaravone to benefit ALS patients outside of these criteria, they also do not establish that it would not. In addition, ALS is a heterogeneously progressive disease that does not adhere neatly to arbitrarily defined categorical stages in clinical practice. This situation would make it extremely unclear as to when one should "withdraw" treatment from patients who progress if the population for whom edaravone was indicated was very narrow. Moreover, there is no immediately obvious mechanistic reason that edaravone would only be expected to be effective in the EESP or Definite/Probable/EESP/2Y populations. Therefore, without any compelling empirical evidence to restrict the indication, my recommendation is that edaravone should be approved for a generally worded ALS claim. The CLINICAL TRIALS section of the Prescribing Information would accurately reflect the clinical trial populations that were studied leading to an approval.

As a final note, it would be incorrect to think of the patient population that was enrolled in Study 19 as representing only a very mild subset of the disease. These subjects would still be capable of having significant impairments as defined by ALSFRS-R scores, as minimum scores of only 2 were required on each of the scale's 12 items. Further, a disease duration of up to 2 years at Screening is fairly substantial in a condition that is often fatal in 2-4 years from diagnosis. %FVC scores of >80% at Screening also do not preclude the enrollment of subjects who could rapidly progress to experience significant respiratory decline, as evidenced by the occurrence of a number of events of certain disease progression involving respiratory involvement during the trial. Therefore, it is inaccurate to conceptualize this population as extremely early in their disease process and therefore not representative of a large percentage of ALS patients in the community.

- *Japanese Population*

  Dr. Breder's review provides a detailed discussion of the information provided by the applicant in support of the generalizability of the current effectiveness data to non-Japanese subjects. This includes a review of the comparability of ALS diagnoses, clinical practice parameters, natural history, edaravone PK, and what is known regarding edaravone effectiveness and safety (in non-ALS populations). The OCP review also finds that the PK of edaravone in Japanese and Caucasian subjects is comparable. Therefore, I agree with Dr. Breder's conclusion that the findings from Study 16 and 19 can be reasonably extrapolated to non-Japanese ALS patients.

8. Safety

Dr. Breder's review notes that a total of 349 subjects 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. The applicant has also provided data from the non-US postmarketing safety database involving patients who were exposed to edaravone for the treatment of AIS or SAH. I agree with Dr. Breder's conclusion that the current safety database is adequate in the context of a rare disease like ALS.

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For the same reasons that are outlined in Section 7 of this memo, 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 if an approval action is taken.

The following are among the key conclusions of Dr. Breder's review of the safety information contained in the application:

- In the placebo-controlled portions of the clinical trials described in the application, 2/184 (1.1%) and 4/184 (2.2%) of subjects died in the placebo and edaravone-treated groups, respectively. There were no deaths in either group in the placebo-controlled portion of Study 19. These deaths were all related to respiratory failure, the most common cause of death in ALS patients.

- In the placebo-controlled portions of the clinical trials described in the application, the incidence of treatment-emergent serious adverse events (SAEs) was lower in the edaravone-treated subjects (32/184[17%]) as compared to placebo (41/184[22%]). Similarly, discontinuations due to AEs were also lower in edaravone treated subjects (4/184[2.2%]) as compared to placebo (10/184[5.4%]).

- The treatment-emergent AE (TEAE) profile of edaravone in the development program was largely similar to that of placebo, with no clear pattern of imbalances in the safety signals between these groups. The following table, reproduced based on the information contained in Dr. Breder's review, summarizes the TEAEs during the placebo-controlled portions of the clinical trials provided with this application that occurred in at least 5% of the edaravone-treated subjects and in a greater frequency than in placebo:

Preferred Term	Placebo (n=184) N(%)	Edaravone (n=184) N(%)
Headache	10 (5.4)	15(8.2)
Dermatitis, contact	6(3.3)	11(6.0)
Eczema	4(2.2)	12(6.5)
Gait disturbance	17(9.2)	23(12.5)
Contusion	16(8.7)	27(14.7)

- The safety information from the open-label extension phases of the placebo-controlled clinical trials is consistent with the placebo-controlled phases, with no new safety signals emerging.

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

- Dr. Breder has also concluded that serious safety events (deaths, serious and/or significant AEs) that were provided from the non-US postmarketing safety information in the AIS and SAH indications indicated a low number of concerning events which were all largely confounded by the common intercurrent findings in these conditions. Dr. Breder notes that the one exception to this conclusion was with respect to hypersensivity/anaphylaxis which

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revealed 10 cases that he believes have a realistic probability of having an association to treatment with edaravone.

The QT-Interdisciplinary Review Team (QT-IRT) reviewer for this application is Dr. Dhananjay Marathe. Dr. Marathe's review concludes that the applicant should conduct a thorough QT (TQT) study for edaravone as a postmarketing requirement (PMR) to exclude small potential QT prolongation effects (10 ms threshold).

9. Advisory Committee Meeting

Not applicable.

10. Pediatrics

Not applicable.

11. Other Relevant Regulatory Issues

- No Good Clinical Practice (GCP) issues were identified during the review of this application.

- Dr. Breder concludes that the applicant has adequately disclosed financial interests/arrangements with clinical investigators.

- The Office of Scientific Investigations (OSI) has investigated six clinical investigator sites, the applicant (Mitsubishi Tanabe Pharma), and the contract research organization (CRO) ^{(b) (4)} All inspection sites were in Japan. No Form 483s were issued. Based on the results of these inspections, OSI concludes that the data submitted by the applicant in support of the pending application from these sits are acceptable and that the studies were conducted adequately.

- The Controlled Substance Staff (CSS) reviewer for this application is Dr. Katherine Bronson. Dr. Bronson concludes that there are no data indicating that edaravone has abuse potential or induces physical dependence.

12. Labeling

Please refer to the final negotiated product label. The following are among the key labeling issues that have been considered during this review:

- The applicant has proposed two WARNINGS AND PRECAUTIONS which do not appear to be supported by the available data (e.g., ^{(b) (4)}).

- The ability of the clinical effectiveness trials that were submitted with the application to support an indication for the treatment of all subjects with ALS, as opposed to a more restricted indication that only reflects the population enrolled in Study 19 (please refer to Section 7 of this memo for a more detailed discussion regarding this topic).

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- The CLINICAL STUDIES section of the labeling should [(b) (4)] contain detailed information related to the results of the analysis of the primary endpoint from Study 19, as this is the only outcome that was both positive and appropriately controlled for Type I error. [(b) (4)]

13. Postmarketing Recommendations

The following are the recommended <u>postmarketing requirements</u>:

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.

14. Recommended Comments to the Applicant

There are no additional recommended comments for the applicant.

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/s/

NICHOLAS A KOZAUER

05/02/2017