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RESEARCH**

APPLICATION NUMBER:

209176Orig1s000

OTHER REVIEW(S)

PMR/PMC Development Template
PMR # 3208-1

NDA # 209176
Product Name: RADICAVA™ (edaravone)

PMR/PMC Description: A carcinogenicity study of edaravone, administered by a clinically relevant route, in mouse.

PMR/PMC Schedule Milestones:	Draft Protocol Submission:	06/30/2017
	Final Protocol Submission:	10/15/2017
	Study Completion:	11/15/2020
	Final Report Submission:	03/15/2021

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

The application is to be approved and an adequate carcinogenicity study in mouse has not been conducted.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

A carcinogenicity study in mouse is required to identify an unexpected, serious risk of adverse effects of edaravone, in accordance with guidance set forth in ICH S1B: *Guidance for Industry S1B Testing for Carcinogenicity of Pharmaceuticals, July 1997*.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

– **Which regulation?**

- Accelerated Approval (subpart H/E)
 Animal Efficacy Rule
 Pediatric Research Equity Act
 FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
 Assess signals of serious risk related to the use of the drug?
 Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?

Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

- Analysis using pharmacovigilance system?

Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A carcinogenicity study of edaravone, administered by a clinically-relevant route, in mouse.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)

-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

- Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

- There is a significant question about the public health risks of an approved drug
- There is not enough existing information to assess these risks
- Information cannot be gained through a different kind of investigation
- The trial will be appropriately designed to answer question about a drug's efficacy and safety, and

The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

(signature line for BLAs)

PMR/PMC Development Template
PMR # 3208-2

NDA/BLA # 209176
Product Name: RADICAVA™ (edaravone)

PMR/PMC Description: A two-year carcinogenicity study of edaravone, administered by a clinically relevant route, in rat.

PMR/PMC Schedule Milestones:

Draft Protocol Submission:	06/30/2017
Final Protocol Submission:	10/15/2017
Trial Completion:	11/15/2020
Final Report Submission:	03/15/2021

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

The application is to be approved and a carcinogenicity study in rat has not been conducted.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

A carcinogenicity study in rat is required to identify an unexpected, serious risk of adverse effects of edaravone, in accordance with guidance set forth in ICH S1B: *Guidance for Industry S1B Testing for Carcinogenicity of Pharmaceuticals, July 1997.*

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?

Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

- Analysis using pharmacovigilance system?

Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A two-year carcinogenicity study of edaravone, administered by a clinically relevant route, in rat.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
 - Are the objectives clear from the description of the PMR/PMC?
 - Has the applicant adequately justified the choice of schedule milestone dates?
 - Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?
- Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

- There is a significant question about the public health risks of an approved drug
- There is not enough existing information to assess these risks

- Information cannot be gained through a different kind of investigation
 - The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
 - The trial will emphasize risk minimization for participants as the protocol is developed
-

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

PMR/PMC Development Template
PMR # 3208-3

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

NDA/BLA# NDA 209176
Product Radicava (edaravone)
Name:

PMR/PMC Description: Conduct a clinical trial to evaluate the effects of hepatic impairment on the pharmacokinetics of edaravone in patients with severe hepatic impairment and demographic-matched (e.g., age, gender, race, weight) healthy subjects who receive a single-dose treatment of edaravone. Please refer to the Guidance for Industry Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling (<https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072123.pdf>)

PMR/PMC Schedule Milestones:	Draft Protocol Submission:	10/31/2017
	Final Protocol Submission:	4/30/2018
	Trial Completion:	12/15/2019
	Final Report Submission:	06/30/2020
	Other:	MM/DD/YYYY

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Edaravone is ready to be approved. This issue is appropriate for a PMR because Amyotrophic Lateral Sclerosis (ALS), is a rare but devastating disease. Only one drug is currently approved for ALS in the U.S. (i.e., riluzole). therefore, there is an unmet medical need. It is expected that the ALS patients with severe hepatic impairment would be a small population. Thus, it is not reasonable to delay the approval of edaravone solely because the data on pharmacokinetic of edaravone are not available in the sub-population with severe hepatic impairment.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The liver is a major organ for elimination of edaravone. Edaravone is metabolized by Phase II enzymes to form a sulfate conjugate and a glucuronide conjugate. Thus, in patients with severe hepatic impairment, the increase in systemic exposure (e.g., C_{max}) to edaravone could be significantly greater than observed in the clinical trials. The potential impact of severe hepatic impairment cannot be fully assessed without pharmacokinetic data in such patients. The proposed PMR aims to provide such data.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?

Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

- Analysis using pharmacovigilance system?

Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Conduct a clinical trial to evaluate the effects of hepatic impairment on the pharmacokinetics of edaravone in patients with severe hepatic impairment and demographic-matched (e.g., age, gender, race, weight) healthy subjects who receive a single-dose treatment of edaravone. Please refer to the Guidance for Industry Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling (<https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072123.pdf>)

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

- Meta-analysis or pooled analysis of previous studies/clinical trials
- Immunogenicity as a marker of safety
- Other (provide explanation)

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)

- Other

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

- There is a significant question about the public health risks of an approved drug
- There is not enough existing information to assess these risks
- Information cannot be gained through a different kind of investigation
- The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

(signature line for BLAs)

A thorough QT study has not yet been performed. Monitoring for QT prolongation in the clinical trials was limited and could not rule out the possibility of a greater than 10 ms increase in QT interval. The Interdisciplinary Review Team for QT Studies recommended a PMR for a Thorough QT study for this product in a review dated 12/19/16.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

- Accelerated Approval (subpart H/E)
 Animal Efficacy Rule
 Pediatric Research Equity Act
 FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
 Assess signals of serious risk related to the use of the drug?
 Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?

Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

- Analysis using pharmacovigilance system?

Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A clinical trial to assess the risk of QT prolongation with edaravone to exclude mean QTc effects greater than 20 ms.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)

-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

- Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

- There is a significant question about the public health risks of an approved drug
- There is not enough existing information to assess these risks
- Information cannot be gained through a different kind of investigation
- The trial will be appropriately designed to answer question about a drug's efficacy and safety, and

The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

(signature line for BLAs)

The application is ready to be approved for a fatal degenerative disease.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The applicant has conducted very limited investigation of dose/response, and has not established whether a ceiling of efficacy has been reached. The sponsor has investigated a dosing regimen with only 10 days of treatment per month, with no apparent scientific justification, and it is possible, if not likely, that greater benefit may be achieved with more frequent dosing. As ALS is fatal degenerative disease, in which the majority of patients die within 2-4 years of diagnosis, a study investigating higher doses and more frequent administration of the drug is important to assess whether greater benefit can be achieved.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

– **Which regulation?**

- Accelerated Approval (subpart H/E)
 Animal Efficacy Rule
 Pediatric Research Equity Act
 FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
 Assess signals of serious risk related to the use of the drug?
 Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?

Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

- Analysis using pharmacovigilance system?

Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Conduct a randomized, double-blind, controlled trial of edaravone in patients with ALS (definite or probable, according to ALS El Escorial Revised Airlie House criteria). Patients should be randomized (1:1:1) to the approved dosing regimen and dosage of edaravone (60 mg), the approved dosage of edaravone (60mg) with a daily or near-daily dosing regimen, or to a dosage of 120 mg of edaravone (a dosage even higher would be desirable if supported by safety data), with a daily or near-daily dosing regimen. The primary efficacy endpoint will be the change in the revised ALS functional rating scale score (ALSFRS-R) from baseline to the end of the study. The study duration will be at least 24 weeks.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E

Radicava (edaravone)

NDA 209176

Dose-response study or clinical trial performed for effectiveness

Nonclinical study, not safety-related (specify)

Other

5. Is the PMR/PMC clear, feasible, and appropriate?

Does the study/clinical trial meet criteria for PMRs or PMCs?

Are the objectives clear from the description of the PMR/PMC?

Has the applicant adequately justified the choice of schedule milestone dates?

Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

There is a significant question about the public health risks of an approved drug

There is not enough existing information to assess these risks

Information cannot be gained through a different kind of investigation

The trial will be appropriately designed to answer question about a drug's efficacy and safety, and

The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

(signature line for BLAs)

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

/s/

SALLY U YASUDA
05/05/2017

**REGULATORY PROJECT MANAGER
PHYSICIAN LABELING RULE (PLR) FORMAT REVIEW
OF THE PRESCRIBING INFORMATION**

Complete for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Labeling Supplements

Application: NDA 209176

Application Type: New NDA

Drug Name(s)/Dosage Form(s): edaravone IV injection

Applicant: Mitsubishi Tanabe Pharma Corporation

Receipt Date: 06/16/16

Goal Date: 2/16/17

1. Regulatory History and Applicant's Main Proposals

This is a program NDA.

2. Review of the Prescribing Information

This review is based on the applicant's submitted Word format of the prescribing information (PI). The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements of Prescribing Information (SRPI)" checklist (see Section 4 of this review).

3. Conclusions/Recommendations

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies, see Section 4 of this review.

All SRPI format deficiencies of the PI will be conveyed to the applicant in the 74-day letter. The applicant will be asked to correct these deficiencies and resubmit the PI in Word format by September 16, 2016. The resubmitted PI will be used for further labeling review.

4. Selected Requirements of Prescribing Information

The Selected Requirement of Prescribing Information (SRPI) is a 41-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

Highlights

See Appendix for a sample tool illustrating Highlights format.

HIGHLIGHTS GENERAL FORMAT

Selected Requirements of Prescribing Information

- YES** 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.

Comment:

- YES** 2. The length of HL must be one-half page or less unless a waiver has been granted in a previous submission. The HL Boxed Warning does not count against the one-half page requirement. Instructions to complete this item: If the length of the HL is one-half page or less, select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page, select “NO” unless a waiver has been granted.

Comment:

- YES** 3. A horizontal line must separate:
- HL from the Table of Contents (TOC), **and**
 - TOC from the Full Prescribing Information (FPI).

Comment:

- YES** 4. All headings in HL (from Recent Major Changes to Use in Specific Populations) must be **bolded** and presented in the center of a horizontal line. (Each horizontal line should extend over the entire width of the column.) The HL headings (from Recent Major Changes to Use in Specific Populations) should be in UPPER CASE letters. See Appendix for HL format.

Comment:

- YES** 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix for HL format.

Comment:

- NO** 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

Comment: *Cross reference under Adverse Reactions is missing.*

- NO** 7. Headings in HL must be presented in the following order:

Heading	Required/Optional
• Highlights Heading	Required
• Highlights Limitation Statement	Required
• Product Title	Required
• Initial U.S. Approval	Required
• Boxed Warning	Required if a BOXED WARNING is in the FPI
• Recent Major Changes	Required for only certain changes to PI*
• Indications and Usage	Required
• Dosage and Administration	Required
• Dosage Forms and Strengths	Required
• Contraindications	Required (if no contraindications must state “None.”)
• Warnings and Precautions	Not required by regulation, but should be present
• Adverse Reactions	Required
• Drug Interactions	Optional
• Use in Specific Populations	Optional
• Patient Counseling Information Statement	Required
• Revision Date	Required

Selected Requirements of Prescribing Information

* RMC only applies to five labeling sections in the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS.

Comment: *The Product Title is missing.*

HIGHLIGHTS DETAILS

Highlights Heading

- YES** 8. At the beginning of HL, the following heading, “**HIGHLIGHTS OF PRESCRIBING INFORMATION**” must be **bolded** and should appear in all UPPER CASE letters.

Comment:

Highlights Limitation Statement

- YES** 9. The **bolded** HL Limitation Statement must include the following verbatim statement: “**These highlights do not include all the information needed to use (insert NAME OF DRUG PRODUCT) safely and effectively. See full prescribing information for (insert NAME OF DRUG PRODUCT).**” The name of drug product should appear in UPPER CASE letters.

Comment:

Product Title in Highlights

- YES** 10. Product title must be **bolded**.

Comment:

Initial U.S. Approval in Highlights

- YES** 11. Initial U.S. Approval must be **bolded**, and include the verbatim statement “**Initial U.S. Approval:**” followed by the **4-digit year**.

Comment:

Boxed Warning (BW) in Highlights

- N/A** 12. All text in the BW must be **bolded**.

Comment:

- N/A** 13. The BW must have a title in UPPER CASE, following the word “**WARNING**” and other words to identify the subject of the warning. Even if there is more than one warning, the term “**WARNING**” and not “**WARNINGS**” should be used. For example: “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”. If there is more than one warning in the BW title, the word “and” in lower case can separate the warnings. The BW title should be centered.

Comment:

- N/A** 14. The BW must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” This statement must be placed immediately beneath the BW title, and should be centered and appear in *italics*.

Comment:

- N/A** 15. The BW must be limited in length to 20 lines. (This includes white space but does not include the BW title and the statement “*See full prescribing information for complete boxed warning.*”)

Selected Requirements of Prescribing Information

Comment:

Recent Major Changes (RMC) in Highlights

- N/A** 16. RMC pertains to only five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. Labeling sections for RMC must be listed in the same order in HL as they appear in the FPI.

Comment:

- N/A** 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section's identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, "Warnings and Precautions, Acute Liver Failure (5.1) --- 8/2015."

Comment:

- N/A** 18. A changed section must be listed under the RMC heading for at least one year after the date of the labeling change and must be removed at the first printing subsequent to the one year period. (No listing should be one year older than the revision date.)

Comment:

Dosage Forms and Strengths in Highlights

- N/A** 19. For a product that has more than one dosage form (e.g., capsules, tablets, injection), bulleted headings should be used.

Comment:

Contraindications in Highlights

- YES** 20. All contraindications listed in the FPI must also be listed in HL. If there is more than one contraindication, each contraindication should be bulleted. If no contraindications are known, must include the word "None."

Comment:

Adverse Reactions in Highlights

- YES** 21. For drug products other than vaccines, the verbatim **bolded** statement must be present: "**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer's U.S. phone number which should be a toll-free number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.**"

Comment:

Patient Counseling Information Statement in Highlights

- YES** 22. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

Selected Requirements of Prescribing Information

- See 17 for PATIENT COUNSELING INFORMATION

If a product **has (or will have)** FDA-approved patient labeling:

- See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling
- See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Comment:

Revision Date in Highlights

- YES** 23. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., “**Revised: 8/2015**”).

Comment:

Selected Requirements of Prescribing Information

Contents: Table of Contents (TOC)

See Appendix for a sample tool illustrating Table of Contents format.

- YES** 24. The TOC should be in a two-column format.
Comment:
- YES** 25. The following heading must appear at the beginning of the TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS.**” This heading should be in all UPPER CASE letters and **bolded**.
Comment:
- YES** 26. The same title for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.
Comment:
- YES** 27. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.
Comment:
- YES** 28. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (for, of, to) and articles (a, an, the), or conjunctions (or, and)].
Comment:
- YES** 29. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.
Comment:
- YES** 30. If a section or subsection required by regulation [21 CFR 201.56(d)(1)] is omitted from the FPI, the numbering in the TOC must not change. The heading “**FULL PRESCRIBING INFORMATION: CONTENTS***” must be followed by an asterisk and the following statement must appear at the end of the TOC: “*Sections or subsections omitted from the full prescribing information are not listed.”
Comment:

Selected Requirements of Prescribing Information

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

- YES** 31. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. (Section and subsection headings should be in UPPER CASE and title case, respectively.) If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

BOXED WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Lactation (if not required to be in Pregnancy and Lactation Labeling Rule (PLLR) format, use "Labor and Delivery")
8.3 Females and Males of Reproductive Potential (if not required to be in PLLR format, use "Nursing Mothers")
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

- NO** 32. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, “[*see Warnings and Precautions (5.2)*].”

Comment: *Text needs to be italicized*

Selected Requirements of Prescribing Information

- N/A** 33. For each RMC listed in HL, the corresponding new or modified text in the FPI must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

- NO** 34. The following heading “**FULL PRESCRIBING INFORMATION**” must be **bolded**, must appear at the beginning of the FPI, and should be in UPPER CASE.

Comment:

BOXED WARNING Section in the FPI

- N/A** 35. All text in the BW should be **bolded**.

Comment:

- N/A** 36. The BW must have a title in UPPER CASE, following the word “**WARNING**” and other words to identify the subject of the warning. (Even if there is more than one warning, the term, “**WARNING**” and not “**WARNINGS**” should be used.) For example: “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”. If there is more than one warning in the BW title, the word “and” in lower case can separate the warnings.

Comment:

CONTRAINDICATIONS Section in the FPI

- YES** 37. If no Contraindications are known, this section must state “None.”

Comment:

ADVERSE REACTIONS Section in the FPI

- YES** 38. When clinical trials adverse reactions data are included (typically in the “Clinical Trials Experience” subsection), the following verbatim statement (or appropriate modification) should precede the presentation of adverse reactions from clinical trials:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.”

Comment:

- YES** 39. When postmarketing adverse reaction data are included (typically in the “Postmarketing Experience” subsection), the following verbatim statement (or appropriate modification) should precede the presentation of adverse reactions:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

Comment:

Selected Requirements of Prescribing Information

PATIENT COUNSELING INFORMATION Section in the FPI

- YES** 40. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION). The reference statement should appear at the beginning of Section 17 and include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Instructions for Use, or Medication Guide). Recommended language for the reference statement should include one of the following five verbatim statements that is most applicable:
- Advise the patient to read the FDA-approved patient labeling (Patient Information).
 - Advise the patient to read the FDA-approved patient labeling (Instructions for Use).
 - Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use).
 - Advise the patient to read the FDA-approved patient labeling (Medication Guide).
 - Advise the patient to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

Comment:

- YES** 41. FDA-approved patient labeling (e.g., Patient Information, Instructions for Use, or Medication Guide) must not be included as a subsection under Section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

Comment:

Selected Requirements of Prescribing Information

Appendix: Highlights and Table of Contents Format

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use **PROPRIETARY NAME** safely and effectively. See full prescribing information for **PROPRIETARY NAME**.

PROPRIETARY NAME (non-proprietary name) dosage form, route of administration, controlled substance symbol
Initial U.S. Approval: YYYY

WARNING: TITLE OF WARNING

See full prescribing information for complete boxed warning.

- Text (4)
- Text (5.x)

RECENT MAJOR CHANGES

Section Title, Subsection Title (x.x) M/201Y
Section Title, Subsection Title (x.x) M/201Y

INDICATIONS AND USAGE

PROPRIETARY NAME is a (insert FDA established pharmacologic class text phrase) indicated for ... (1)

Limitations of Use: Text (1)

DOSAGE AND ADMINISTRATION

- Text (2.x)
- Text (2.x)

DOSAGE FORMS AND STRENGTHS

Dosage form(s): strength(s) (3)

CONTRAINDICATIONS

- Text (4)
- Text (4)

WARNINGS AND PRECAUTIONS

- Text (5.x)
- Text (5.x)

ADVERSE REACTIONS

Most common adverse reactions (incidence > x%) are text (6.x)

To report **SUSPECTED ADVERSE REACTIONS**, contact name of manufacturer at toll-free phone # or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Text (7.x)
- Text (7.x)

USE IN SPECIFIC POPULATIONS

- Text (8.x)
- Text (8.x)

See 17 for **PATIENT COUNSELING INFORMATION** and FDA-approved patient labeling **OR** and Medication Guide.

Revised: M/201Y

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: TITLE OF WARNING

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

2.1 Subsection Title

2.2 Subsection Title

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

5.1 Subsection Title

5.2 Subsection Title

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

6.2 Immunogenicity

6.2 or 6.3 Postmarketing Experience

7 DRUG INTERACTIONS

7.1 Subsection Title

7.2 Subsection Title

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

8.2 Lactation (if not required to be in PLLR format use Labor and Delivery)

8.3 Females and Males of Reproductive Potential (if not required to be in PLLR format use Nursing Mothers)

8.4 Pediatric Use

8.5 Geriatric Use

8.6 Subpopulation X

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

9.2 Abuse

9.3 Dependence

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

12.2 Pharmacodynamics

12.3 Pharmacokinetics

12.4 Microbiology

12.5 Pharmacogenomics

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

13.2 Animal Toxicology and/or Pharmacology

14 CLINICAL STUDIES

14.1 Subsection Title

14.2 Subsection Title

15 REFERENCES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

* Sections or subsections omitted from the full prescribing information are not listed.

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/s/

JACK DAN
05/05/2017

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy**

PATIENT LABELING REVIEW

Date: April 19, 2017

To: William Dunn, M.D.
Director
Division of Neurology Products (DNP)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

Mathilda Fienkeng, PharmD, RAC
Team Leader
Office of Prescription Drug Promotion (OPDP)

From: Marcia Williams, PhD
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

Sharon W. Williams, MSN, BSN, RN
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Aline M. Moukhtara, RN, MPH
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Patient Package Insert (PPI)

Drug Name (established name): RADICAVA (edaravone injection)

Dosage Form and Route: for intravenous use

Application Type/Number: NDA 209176

Applicant: Mitsubishi Tanabe Pharma Development America, Inc.

1 INTRODUCTION

On June 16, 2016, Mitsubishi Tanabe Pharma Development America, Inc. submitted for the Agency's review a new drug application (NDA) for RADICAVA (edaravone injection), for intravenous use. RADICAVA (edaravone injection), for intravenous use is indicated for the treatment of amyotrophic lateral sclerosis (ALS).

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Neurology Products (DNP) on April 10, 2107 and June 28, 2016, respectively, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for RADICAVA (edaravone injection), for intravenous use.

2 MATERIAL REVIEWED

- Draft RADIVICA (edaravone injection), for intravenous use PPI received on June 16, 2016, and received by DMPP on April 11, 2017.
- Draft RADIVICA (edaravone injection), for intravenous use PPI received on June 16, 2016, and received by OPDP on April 7, 2017.
- Draft RADIVICA (edaravone injection), for intravenous use Prescribing Information (PI) received on June 16, 2016, revised by the Review Division throughout the review cycle, and received by DMPP on April 11, 2017.
- Draft RADIVICA (edaravone injection), for intravenous use Prescribing Information (PI) received on June 16, 2016, revised by the Review Division throughout the review cycle, and received by OPDP on April 7, 2017.

3 REVIEW METHODS

In 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the PPI document using the Arial font, size 10.

In our collaborative review of the PPI we:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information

- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

4 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

SHARON W WILLIAMS
04/19/2017

ALINE M MOUKHTARA
04/19/2017

MARCIA B WILLIAMS
04/19/2017

LASHAWN M GRIFFITHS
04/20/2017

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

*****Pre-decisional Agency Information*****

Memorandum

Date: April 11, 2017

To: Billy Dunn, MD, Director
Division of Neurology Products (DNP)

Tracy Peters, PharmD, Associate Director for Labeling, DNP

Jack Dan, RPh, Regulatory Project Manager, DNP

From: Aline Moukhtara, RN, MPH, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Through: Mathilda Fienkeng, PharmD, RAC, Team Leader, OPDP

Subject: **NDA 209176**
OPDP labeling comments for RADICAVA (edaravone injection), for intravenous use

In response to DNP's consult request dated June 28, 2016, OPDP has reviewed the proposed Package Insert (PI), Patient Package Insert (PPI), and carton and container labeling for Radicava.

PI: OPDP's comments are based on the substantially complete version of the draft PI obtained from DNP Sharepoint on April 10, 2017, and are provided below.

PPI: A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed, and comments on the proposed PPI will be provided under a separate cover.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on October 27, 2016, and we do not have any comments.

If you have questions, please contact Aline Moukhtara at (301) 796-2841 or Aline.Moukhtara@fda.hhs.gov.

OPDP appreciates the opportunity to provide comments.

11 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

ALINE M MOUKHTARA
04/11/2017



MEMORANDUM
Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: March 1, 2017

To: Billy Dunn, M.D., Director
Division of Neurology Products (DNP)

Through: Silvia Calderon, Ph.D., Senior Pharmacologist
Controlled Substance Staff (CSS)

From: Katherine Bonson, Ph.D., Pharmacologist
Controlled Substance Staff (CSS)

Subject: Edaravone (RADICAVA, 60 mg/day, i.v.)
NDA 209,176 (IND 126,396)
Indication: Treatment of Amyotrophic Lateral Sclerosis
Sponsor: Mitsubichi Tanabe Pharma Group

Materials reviewed: NDA submission (6/16/16)

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I. SUMMARY

A. Background

The Division of Neurology Products (DNP) consulted CSS regarding an abuse potential assessment of edaravone under NDA 209,176. Edaravone is being developed by Mitsubishi Tanabe Pharma Group for the treatment of (b) (4) Amyotrophic Lateral Sclerosis (ALS). The Sponsor concludes from the data submitted that edaravone does not have abuse potential and should not be scheduled under the Controlled Substances Act.

The Sponsor states that edaravone (MCI-186) is “a compound with free radical-scavenging effects”. The drug was approved in 2001 in Japan for treatment of acute ischemic stroke (AIS) and was subsequently approved in Japan in 2015 for the treatment of ALS. The dosage regimen is a daily 60 mg i.v. infused over 60 minutes, for 14 consecutive days, followed by a 2-week drug-free period (Cycle 1), and then administration for a total of 10 days over 2 weeks followed by a 2-week drug-free period (Cycle 2 and thereafter). Edaravone received orphan designation from FDA for the treatment of ALS on May 12, 2015.

B. Conclusions

CSS reviewed the abuse-related data in the NDA for edaravone and concluded that the drug does not have abuse potential. These conclusions were based on results from the studies showing that edaravone:

- Does not bind to CNS sites associated with abuse potential.
- Can cross the blood-brain barrier into the cerebral spinal fluid, but it does not penetrate into brain tissue.
- Does not produce general behavioral changes.
- Does not produce rewarding properties in rats, based on its lack of ability to produce conditioned place preference. However, it did appear to produce some degree of conditioned place aversion.
- Produces self-administration in monkeys that was generally similar to that produced by placebo or at a rate that was intermediate between placebo and pentobarbital. Sporadically, some monkeys self-administered edaravone to the same degree as that produced by pentobarbital. However, since only 4 monkeys were used in these studies, the study power is low.
- Does not produce physical dependence in rats after chronic administration.
- Does not produce any abuse-related adverse events (including euphoria-related AEs) in 1700 subjects exposed to edaravone.

C. Recommendations

Given that edaravone does not exhibit abuse potential and dependence liability, CSS recommends that:

- Edaravone not be scheduled under the Controlled Substances Act
- Section 9.0 (Drug Abuse and Dependence) of the label for edaravone may be eliminated.

II. Discussion

A. Chemistry

Edaravone is known chemically as methyl phenyl pyrazolone; 3H-pyrazol-3-one; 2,4-dihydro-5-methyl-2-phenyl- (CAS). It is also known as 1-Phenyl-3-methylpyrazol-5-one; norantipyrine; or norphenazone. The CAS number of edaravone is 89-25-8. The formula of edaravone is C₁₀H₁₀N₂O and its molecular weight is 174.2. It is freely soluble in acetic acid (100), methanol or ethanol (99.5), and slightly soluble in water or diethyl ether.

B. Nonclinical Pharmacology

Receptor Binding Studies (Study #P-1 and AB 32785)

Receptor binding studies showed that when edaravone was evaluated at 10 micromolar concentrations at 79 CNS receptors, channels and transporters, the drug did not show affinity greater than 20% for any site, including ones associated with abuse potential, such as μ , δ , and κ opioid; GABA-A and GABA-B; NMDA, glutamate and glycine; cannabinoid (CB1); dopamine (D1, D2, and D3); nicotine (acetylcholine); serotonin (5HT1A, 2A, 3, 4); sigma; sodium, calcium channels; transporters for dopamine, norepinephrine, serotonin and GABA.

The Sponsor notes that the 10 micromolar concentration that was tested is ~20 times higher than the estimated human plasma concentration of unbound edaravone of 88 ng/mL following the proposed clinical dose of 60 mg/60 min infusion (C_{max} of edaravone = 1049 ng/mL estimated by PPK and human protein binding rate = 91.6%). Thus, C_{max} of unbound edaravone = 1049 ng/mL x (100.0% – 91.6% = 8.4%) = 88 ng/mL).

CNS Penetration in Pharmacokinetic Studies (Study #A-1, A-8, B020989)

Two distribution studies were conducted to evaluate tissue distribution of [¹⁴C]edaravone by measuring total radioactivity through excised tissue radioactivity and whole-body autoradiography. In one study, a single intravenous dose of [¹⁴C]edaravone was given at a dose of 2 mg/kg/day to male and female rats. Measurements were taken from 5 minutes to 192 hours after a single dose. In the other study, [¹⁴C]edaravone was given to

male rats for 21 days at the same dose of 2 mg/kg/day. Measurements were taken from 24 hours on the first day to 24 hours on the last day after 21 days of repeated doses.

In these studies, radioactivity was rapidly distributed systemically, especially into the kidney and aorta but was poorly distributed into brain, spinal cord, fat pad, bone, testes, seminal vesicles, uterus, and ovaries at 5 minutes. Concentrations of radioactivity in brain of male and female rats were 0.59 µg eq./g and 0.62 µg eq./g, respectively, which were 1/16 and 1/18 times that of plasma concentrations.

In an absorption study in dogs, the ratio of plasma to cerebral spinal fluid (CSF) after a 3 hour infusion of edaravone at an infusion rate of 1 mg/kg/hr was 60% of plasma edaravone. This demonstrates the edaravone crosses the blood-brain barrier into the CSF.

These three studies show that under acute and chronic administration of radiolabeled edaravone, drug derived radioactivity did enter the CSF but did not significantly penetrate the brain.

Animal Behavioral Studies

General Behavioral Evaluations

Edaravone reduced spontaneous movement in rodents at intravenous doses ≥ 30 mg/kg when animals were tested using the wheel cage and open field methods. These high doses also produced blepharoptosis and lacrimation. The 30 mg/kg dose (i.v.) produced plasma levels in mice and rats that were (respectively) 67 and 120 times greater than the plasma levels produced at the proposed therapeutic dose.

Edaravone did not produce any changes in behavioral responses in the following tests:

- pentobarbital sodium-induced anesthesia
- anticonvulsive effect and convulsive effect
- electroencephalogram
- spinal reflex and motor coordination
- cataleptic effect

These data demonstrate that edaravone does not produce overt behavioral changes after intravenous doses that are equivalent to many times greater than the proposed therapeutic dose.

Conditioned Place Preference Study (Study # 1P111)

Mice were trained in the conditioned place preference (CPP) test using a shuttle box with two compartments that were visually different. Animals received edaravone (3, 10 and 30 mg/kg, i.v.), cocaine as the positive control (1 and 2 mg/kg, i.v.), and vehicle. The doses of edaravone produce plasma levels that are 2.2, 7.4 and 67 times greater than the plasma levels produced by the proposed therapeutic dose of 60 mg/60 min infusion in humans.

In initial sessions for CPP, mice were allowed to explore the entire chamber. Animals were observed to determine which side they preferred. During conditioning training, mice were given the test substance and were confined to the non-preferred compartment of the test chamber. On the next day, mice were given vehicle and confined to the preferred compartment. Animals alternated this procedure for 6 days.

Animals were also trained in conditioned place aversion (CPA). In these tests, animals underwent the same procedures as those described above for CPP but were placed in the opposite chamber (e.g., drug paired with preferred side, vehicle paired with non-preferred side).

During the test phase, each mouse was placed in the center of the test chamber without the partitions separating the two compartments. Animals were not treated with drug or vehicle prior to testing. Animals were allowed 15 minutes in the test chamber and the amount of time spent in each compartment was measured.

Animals that had been trained with cocaine spent more time on the cocaine-associated side than on the vehicle-associated side. In contrast, animals that had been trained with edaravone spent more time on the vehicle side, regardless of whether they had been trained in the CPP or the CPA procedure.

These data demonstrate that edaravone produced dose-dependent conditioned place aversion but did not produce conditioned place preference. This suggests that edaravone produces unpleasant drug effects, but no rewarding responses.

Self-Administration Study (Study # PRL-62A)

Gross Behavioral Observations

Five male monkeys were used to evaluate gross behavioral changes in response to edaravone at 16, 32, 64, and 128 mg/kg (i.v.). In each test session, 4 of the 5 monkeys were used per dose. Animals were observed before and at 0.25, 0.50, 1, 2, 3 and 4 hours after drug administration for gross behavior and pupil size.

Self-Administration Tests

Four male monkeys with previous experience self-administering pentazocine and pentobarbital were used to evaluate edaravone for reinforcing properties. Animals were first provided access to saline, to confirm that they would not self-administer saline more than 10 times/day for 7 days. Then animals were provided with access to pentobarbital (1 mg/kg/infusion, i.v.) to confirm that they would self-administer a drug with known rewarding properties. Monkeys were limited to 30 infusions/session for safety reasons. Animals were returned to saline access as soon as their self-administration of pentobarbital was greater than that of saline for 5 consecutive days. Edaravone access

began as soon as animals demonstrated they would not self-administer saline more than 10 times/day for 7 days.

Edaravone was tested at 1, 4, and 8 mg/kg/infusion (i.v.) for 23 hour periods over 2-4 weeks. In a previous pharmacokinetic study, single bolus infusions of these doses produced plasma levels that were ~3, 15, and 30 times higher than the estimated plasma concentration of edaravone after the proposed clinical dose of 60 mg/subject for 60 min infusion in humans.

Over the drug access period, animals were monitored for general behavior, feeding and fecal production. At the end of the edaravone access period, animals were returned to saline, then to pentobarbital, and finally to saline again. During this last phase, animals were also monitored for withdrawal behaviors.

Results

There were no overt behavioral changes at the 16 mg/kg dose of edaravone. As the dose increased to 128 mg/kg, there were some increasing signs of aggression, retching, vomiting, salivation and ataxia. The majority of behaviors subsided 15 minutes after initial drug administration.

During the self-administration testing, animals received fewer than 10 infusions/session for saline. When monkeys had access to pentobarbital, they typically self-administered the maximum allowable amount of 30 infusions/session. When monkeys had access to edaravone, there were occasional days during which the animals self-administered the drug to the same degree as they did for pentobarbital. Generally, this ranged from 13-18 infusions/session, with rare occasions in which there were 28-32 infusions/session. However, on the majority of test days, the responding for edaravone was similar to that for placebo. There were also occasions on which placebo produced high self-administration.

These data suggest the possibility that edaravone produces some positive effects. However, the study has very low statistical power since only 4 animals were tested.

Physical Dependence Study (Study #3P215)

In the physical dependence study, rats underwent the same experimental method as was used in the pilot study, except that the drug administration was lengthened. Animals (n = 8) received edaravone in a drug-food admixture for 46 days. The initial dose was 1 mg drug per gram of food that was increased over the course of the study to 12 mg drug per gram of food. The highest dose of 12 mg/gm food produces unbound plasma exposure up to 760 ng/ml, which is 8.6 times greater than the estimated plasma exposure in humans after the proposed clinical dose of 60 mg/subject following a 60 min infusion administration. Barbitol (0.5 to 6.0 mg/gm food over 34 days) was used as the positive control in another group of animals (n = 8). Regular chow food was given to rats in the placebo group. At the end of the dosing period, rats were either abruptly discontinued

from edaravone or were treated with naloxone. They were then observed for the appearance of withdrawal signs for 7 days.

Rats that had been treated chronically with barbital and underwent drug discontinuation experienced moderate to severe fascicular-twitching, tremors, and jerking, and death. These animals also showed significantly greater weight loss compared to the edaravone group and to the placebo group.

In contrast, discontinuation of edaravone did not produce any behavioral or physical symptoms. This group also showed no weight loss during the discontinuation period. This lack of withdrawal behaviors was also observed in the group of rats that received placebo. Overall, there were no significant differences between edaravone and placebo in terms of withdrawal observations.

These data show that chronic administration of edaravone at doses that are ~9 times the proposed therapeutic dose does not produce a withdrawal syndrome. This shows that edaravone does not produce physical dependence.

C. Adverse Events Reported in Clinical Efficacy and Safety Studies

The Sponsor conducted 5 clinical studies (1 Phase II and 4 Phase III) with edaravone in ALS patients. The Sponsor also conducted 5 clinical pharmacology studies in healthy volunteers, 9 clinical studies for acute ischemic stroke (AIS), and 3 clinical studies for subarachnoid hemorrhage. A total of 1700 subjects were exposed to edaravone (100 healthy subjects, 350 patients diagnosed with ALS, 860 AIS patients, and 390 subarachnoid hemorrhage patients)

There were no abuse-related adverse events (AEs) that were reported at a rate greater than that observed for placebo during any of the clinical studies in healthy volunteers or in patients. This includes AE reports for anxiety, insomnia, and somnolence. More importantly, there were no AEs showing euphoric or drug-liking effect such as elevated mood, mood alteration, or feeling intoxicated. No hallucinations were reported in any study.

These data show that in humans, edaravone does not produce any abuse-related signals suggesting that it has abuse potential.

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/s/

KATHERINE R BONSON
03/01/2017

SILVIA N CALDERON
03/01/2017

Clinical Inspection Summary

Date	01/31/2017
From	Cara Alfaro, Pharm.D., Clinical Analyst, GCPAB/DCCE/OSI Susan Thompson, M.D., Team Leader, GCPAB/DCCE/OSI Kassa Ayalew, M.D., M.P.H., Branch Chief, GCPAB/DCCE/OSI
To	Jack Dan, Regulatory Project Manager DNP Christopher Breder, M.D., Medical Officer DNP
NDA #	209176
Applicant	Mitsubishi Tanabe Pharma Corp
Drug	Edaravone
NME	Yes
Therapeutic Classification	Free-radical scavenger
Proposed Indication(s)	Treatment of amyotrophic lateral sclerosis
Consultation Request Date	7/25/2016
Summary Goal Date	2/17/2017
Action Goal Date	3/17/2017
PDUFA Date	6/16/2017

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

For NDA 209176, six clinical investigator sites, the sponsor (Mitsubishi Tanabe Pharma), and the CRO (b)(4) were inspected. All inspection sites were in Japan. No Form FDA 483s were issued. Based on the results of these inspections, the data submitted by the sponsor in support of the pending application for these sites are acceptable and the studies were conducted adequately.

Five of the clinical investigator inspections and the sponsor inspection have been classified as No Action Indicated (NAI) based upon review of the Establishment Inspection Reports (EIR). One of the clinical investigator inspections (Morita) and the CRO inspection are preliminarily classified as (b)(5); EIRs are pending for these inspections. An addendum to this Clinical Inspection Summary will be generated if conclusions change upon receipt and review of these EIRs.

II. BACKGROUND

Edaravone (NDA 209176) is being developed for the treatment of amyotrophic lateral sclerosis (ALS). The sponsor submitted two Phase 3 studies considered important in evaluating the efficacy and safety of edaravone for the treatment of ALS. Study MCI-186-16 did not demonstrate efficacy in the prespecified study population but did demonstrate efficacy in a subpopulation of less severe ALS subjects. Study MCI-186-19, considered the pivotal study, evaluated the efficacy and safety of edaravone in this less severely affected ALS population.

Protocol MCI-186-16

Title: A double-blind, parallel-group, placebo-controlled, phase III confirmatory study of MCI-186 (edaravone) for the treatment of amyotrophic lateral sclerosis

Subjects and Sites: 206 subjects were enrolled in 29 sites in Japan

Study Initiation: May 8, 2006

Last Subject Completed: September 9, 2008

This was a double-blind, parallel group study of edaravone (60 mg once daily) compared to placebo in subjects with ALS. The primary efficacy endpoint was the change from baseline to Cycle 6 (24 weeks) in the ALSFRS-R score. The sponsor reported a mean change of -5.3 in the edaravone group and -6.0 in the placebo group, which was not statistically significant ($p = 0.3476$). The sponsor evaluated efficacy in two subgroups of subjects, Efficacy Expected Sub-population (EESP) and definite or probable ALS and EESP and onset less than 2 years (definite/EESP/2Y) and reported statistically significant results favoring edaravone compared to placebo for both subgroups. Based on these analyses, the sponsor chose these subpopulations of less severe ALS to inform the study design of their pivotal Phase 3 study, MCI-186-19.

Protocol MCI-186-19

Title: A phase III, double-blind, parallel-group study of edaravone (MCI-186) for the treatment of amyotrophic lateral sclerosis (second confirmatory study)

Subjects and Sites: 137 subjects were enrolled in 26 sites in Japan

First Subject Enrolled: November 28, 2011

Last Subject Completed: September 3, 2014

This was a double-blind, parallel group study of edaravone (60 mg once daily) compared to placebo in subjects with ALS. The primary efficacy endpoint was the change from baseline to Cycle 6 (24 weeks) in the ALSFRS-R score. The sponsor reported a Least Squares (LS) mean change of -5.0 in the edaravone group and -7.5 in the placebo group with a LS mean difference of 2.49 ($p = 0.0013$) favoring edaravone.

Inspections of clinical sites were considered essential to verify the data submitted for this application. Clinical sites for inspection were chosen primarily based on the numbers of subjects enrolled at the site and/or site-specific efficacy effect size. The focus of the clinical site inspections was adherence to protocols (e.g. inclusion/exclusion criteria), protocol deviations, documentation of informed consent prior to subject participation, reporting of adverse events, maintenance of the study blind, and verification of the primary and key secondary efficacy endpoints.

III. RESULTS (by site)

Site #, Name of CI, Address, Country if non-U.S. or City, State if U.S.	Protocol # and # of Subjects	Inspection Dates	Classification
Site #4 Mitsuya Morita, M.D. 3311-1, Yakushiji Shimotsuke-shi, Tochigi 329-0498 Japan	MCI-186-19 Subjects: 10	01/16/2017 to 01/20/2017	(b) (5) *
Site #8 Hiroyuki Ishiura, M.D., Ph.D. 7-3-1, Hongo Bunkyo-ku, Tokyo, 113-8655 Japan	MCI-186-19 Subjects: 7	10/24/2016 to 10/28/2016	NAI
Site #12 Naoki Atsuta, M.D., Ph.D. 65, Tsurumaicho Showa-ku Nagoya-shi, Aichi 466-8560 Japan	MCI-186-19 Subjects: 8	10/31/2016 to 11/04/2016	NAI
Sites #6300391 and #16 Koji Abe, M.D., Ph.D. 2-5-1 Shikatacho Kita-ku, Okahama-shi, Okayama 700-8558 Japan	MCI-186-16 Subjects: 12 MCI-186-19 Subjects: 12	10/24/2016 to 11/02/2016	NAI
Site #2301465 Takashi Imai, M.D. 100, Aza Kassenbara, Takase, Yamamotocho Watari-gun, Miyagi 989-2202 Japan	MCI-186-16 Subjects: 7	11/16/2016 to 11/21/2016	NAI
Site #8102393 Shizuma Kaku, M.D. 4-5, Sugu Kita Kasuga-shi, Fukuoka 816-0864 Japan	MCI-186-16 Subjects: 6	10/31/2017 to 11/04/2017	NAI
(b) (4), (b) (5)			

Site #, Name of CI, Address, Country if non-U.S. or City, State if U.S.	Protocol # and # of Subjects	Inspection Dates	Classification
Mitsubishi Tanabe Pharma Corporation 17-10, Nihonbashi-Koamicho Chuo-ku, Tokyo 103-8405 Japan	MCI-186-16 MCI-186-19	11/7/2016 to 11/11/2016	NAI

Compliance Classifications

NAI = No Action Indicated; no deviation from regulations.

VAI = Voluntary Action Indicated; deviation(s) from regulations.

OAI = Official Action Indicated; significant deviations from regulations. Data may be unreliable.

*Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending. Final classification occurs when the post-inspectional letter has been sent to the inspected entity.

1. **Clinical Investigator:** Mitsuya Morita, M.D.; Tochigi, Japan; Site #4
Protocol MCI-186-19 was not conducted under an IND.

For Protocol MCI-186-19, seventeen subjects were screened, ten subjects were enrolled, and eight subjects completed the study. The field investigator did not provide information on the two subjects who discontinued the study. Per sponsor data listings, these subject discontinuations were due to “withdrawal by subject” and “adverse event/aspiration pneumonia/fatal”.

A Form FDA 483 was not issued at the conclusion of the inspection. The field investigator discussed a number of issues with the clinical investigator including (b) (5)

The available summary data from the field investigator did not identify regulatory issues for this clinical investigator inspection. The study appears to have been conducted adequately and the data generated by this site appear acceptable in support of the indication. If this conclusion changes upon receipt and review of the EIR, an addendum to this CIS will be provided.

2. **Clinical Investigator:** Hiroyuki Ishiura, M.D., Ph.D.; Tokyo, Japan; Site #8
Protocol MCI-186-19 was not conducted under an IND.

For Protocol MCI-186-19, nine subjects were screened, seven subjects were enrolled, and five subjects completed the study. The field investigator did not provide information on the two subjects who discontinued the study. Per sponsor data listings, these subject discontinuations were due to “withdrawal by subject” and “other”.

Signed informed consent forms were present for all subjects who were enrolled to participate in the study prior to participation. Records were reviewed for all nine subjects and included but were not limited to source documents, CRFs, inclusion/exclusion criteria, adverse event reports, concomitant medications, IRB/sponsor communications, delegation logs, training records, enrollment logs, test article accountability, protocol deviations, and primary and secondary efficacy data. Financial disclosure forms were signed after the study was completed. The sponsor originally intended to seek approval in Japan only, and financial disclosure forms were not required prior to the start of the study. The sponsor performed monitoring for the site. The field investigator was unable to view monitoring reports as they were stored at the sponsor site.

A Form FDA 483 was not issued. The study appears to have been conducted adequately and the data generated by this site appear acceptable in support of the indication.

3. **Clinical Investigator:** Naoki Atsuta, M.D.; Aichi, Japan; Site #12
Protocol MCI-186-19 was not conducted under an IND.

For Protocol MCI-186-19, the field investigator did not note the disposition of subjects. Per data listings, nine subjects were screened, eight subjects were enrolled, and five subjects completed the study. The three subject discontinuations were due to “withdrawal by subject” in two subjects and “disposition event, progressive disease” in one subject.

Signed informed consent forms were present for all subjects who were enrolled to participate in the study prior to participation. Records were reviewed for all subjects and included but were not limited to source documents, CRFs, inclusion/exclusion criteria, adverse event reports, concomitant medications, IRB/sponsor communications, delegation logs, training records, enrollment logs, test article accountability, protocol deviations, and primary and secondary efficacy data. Financial disclosure forms were signed after the study was completed. The sponsor originally intended to seek approval in Japan only and financial disclosure forms were not required prior to the start of the study. The sponsor performed monitoring for the site. The field investigator was unable to view monitoring reports as they were stored at the sponsor site.

A Form FDA 483 was not issued. The study appears to have been conducted adequately and the data generated by this site appear acceptable in support of the indication.

4. **Clinical Investigator:** Koji Abe, M.D., Ph.D.; Okayama, Japan; Sites #16 and #6300391
Protocols MCI-186-16 and MCI-186-19 were not conducted under an IND.

For Protocol MCI-186-16, nineteen subjects were screened, twelve subjects were enrolled, and eleven subjects completed the study. One subject discontinued per subject request.

For Protocol MCI-186-19, fifteen subjects were screened, twelve subjects were enrolled, and twelve subjects completed the double-blind phase of the study.

Signed informed consent forms were present for all subjects who were enrolled to participate in the study prior to participation. Records reviewed included but were not limited to source documents, inclusion/exclusion criteria, adverse event reports, concomitant medications, IRB/sponsor communications, training records, enrollment logs, test article accountability, protocol deviations, and primary and secondary efficacy data. Financial disclosure forms were signed between September and November 2015, after the study was completed. The sponsor originally intended to seek approval in Japan only and financial disclosure forms were not required prior to the start of the study. The Sponsor performed monitoring for the site. The field investigator was unable to view monitoring reports as they were stored at the Sponsor site. The Sponsor provided a listing of monitoring dates and monitor names.

A Form FDA 483 was not issued. The study appears to have been conducted adequately and the data generated by this site appear acceptable in support of the indication.

5. Clinical Investigator: Takashi Imai, M.D.; Miyagi, Japan; Site #2301465
Protocol MCI-186-16 was not conducted under an IND.

For Protocol MCI-186-16, nine subjects were screened, seven subjects were enrolled, and seven subjects completed the study.

Signed informed consent forms were present for all subjects who were enrolled to participate in the study prior to participation. Records were reviewed for all enrolled subjects and included but were not limited to source documents, CRFs, inclusion/exclusion criteria, adverse event reports, concomitant medications, IRB/sponsor communications, delegation logs, training records, enrollment logs, test article accountability, protocol deviations, and primary and secondary efficacy data. Financial disclosure forms were signed after the study was completed. The sponsor originally intended to seek approval in Japan only and financial disclosure forms were not required prior to the start of the study. The sponsor performed monitoring for the site. Monitoring reports are kept by the sponsor and were not available at the site.

A Form FDA 483 was not issued. The study appears to have been conducted adequately and the data generated by this site appear acceptable in support of the indication.

6. Clinical Investigator: Shizuma Kaku, M.D.; Fukuoka, Japan; Site #8102393
Protocol MCI-186-16 was not conducted under an IND.

For Protocol MCI-186-16, seven subjects were screened, six subjects were enrolled, and four subjects completed the study. Two subjects discontinued the study due to disease progression.

Signed informed consent forms were present for all subjects who were enrolled to participate in the study prior to participation. Copies of the signature page of the ICFs

were available in subject charts. The clinical investigator stated that sites do not keep a copy of the entire ICF and the original signed ICFs are given to the subjects. Records were reviewed for all subjects and included but were not limited to source documents, CRFs, adverse event reports, concomitant medications, IRB/sponsor communications, IRB approval of task delegations, training records, enrollment logs, test article accountability, protocol deviations, and primary and secondary efficacy data.

Financial disclosure forms were signed after the study was completed. The sponsor originally intended to seek approval in Japan only and financial disclosure forms were not required prior to the start of the study. The sponsor performed monitoring for the site. Monitoring logs are not a requirement in Japan and were not required by the sponsor. Monitoring reports are kept by the sponsor and were not available at the site. The original hospital where the study took place was torn down in 2014, so no original facilities were available for the field investigator to observe.

A Form FDA 483 was not issued. Inspectional discussion items included administration of study drug by a ward nurse who was not on the delegation log. The clinical investigator stated that current studies do include these personnel on the delegation log. Some subjects are seen in the emergency room and they make an exception for these subjects and the emergency room staff is trained in advance of the trial. Documents were available indicating that training of staff at the emergency room was done. The field investigator did not note how frequently this occurred at this site. The field investigator also noted that there was no signed ICF kept as a record in the chart. The clinical investigator stated that the sponsor sets the requirement about whether a copy of the ICF should be retained in the records; some domestic (Japan) studies do not have this requirement.

The study appears to have been conducted adequately and the data generated by this site appear acceptable in support of the indication.

7. Clinical Research Organization:

(b) (4)

This CRO was contracted by Mitsubishi Tanabe Pharma Corporation to provide clinical monitoring for Protocol MCI-186-16. This CRO was contracted to provide these services for an approximate 10-month period, thereafter, Mitsubishi Tanabe Pharma Corporation provided monitoring services.

Monitoring files for ten clinical sites were reviewed. A Form FDA 483 was not issued. Inspectional findings discussed with the CRO included

(b) (5)

The available summary data from the field investigator did not identify regulatory issues for this CRO inspection. The study appears to have been monitored adequately and the data generated by this site appear acceptable in support of the indication. If this conclusion changes upon receipt and review of the EIR, an addendum to this CIS will be provided.

8. **Sponsor:** Mitsubishi Tanabe Pharma Corporation; 17-10, Nihonbashi-Koamicho; Chuo-ku, Tokyo, Japan

This inspection covered sponsor practices related to Protocols MCI-186-16 and MCI-186-19. Regulatory documents for three clinical sites (Imai/Site #2301465, Kaku/Site #8102393, and Abe/Site #6300391) participating in Protocol MCI-186-16 and four clinical sites (Abe/Site #16, Morita/Site #4, Ishiura/Site #8, and Atsuta/Site #12) participating in Protocol MCI-186-19 were reviewed.

Documentation reviewed included written agreements with vendors and CROs, selection of monitors, monitor training, monitoring procedures, monitor reports; Quality Assurance (QA) including audit plan; clinical investigator/site selection procedures; adverse event reporting and protocol deviations; data collection and handling; electronic records and handling; SOPs; IRB approvals; and test article accountability. Financial disclosure forms were not maintained since this study was not performed under an IND and these forms are not required in Japan. Financial disclosure forms were added to the records retroactively for each of the clinical sites.

A Form FDA 483 was not issued. No significant regulatory issues were identified. The studies appear to have been conducted adequately and the data generated by the sponsor appear acceptable in support of the indication.

{See appended electronic signature page}

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CARA L ALFARO

01/31/2017

PM filled out general consult request rather than request for clinical inspections.

SUSAN D THOMPSON

01/31/2017

KASSA AYALEW

02/01/2017

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review: January 30, 2017
Requesting Office or Division: Division of Neurology Products (DNP)
Application Type and Number: NDA 209176
Product Name and Strength: Radicava (edaravone) injection,
0.3 mg/mL
Total Product Strength: 30 mg/100 mL
Product Type: Single-ingredient
Rx or OTC: Rx
Applicant/Sponsor Name: Mitsubishi Tanabe
Submission Date: June 16, 2016; September 13, 2016; January 19, 2017
OSE RCM #: 2016-1431
DMEPA Primary Reviewer: Ebony Whaley, PharmD, BCPPS
DMEPA Team Leader: Lolita White, PharmD

1 REASON FOR REVIEW

This review evaluates the proposed carton labeling, container labels, Prescribing Information, and Medication Guide for Radicava (edaravone) injection, NDA 209176, submitted on June 16, 2016. The Division of Neurology Products (DNP) requested that we review the proposed labels and labeling for areas of vulnerability related to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C – N/A
ISMP Newsletters	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F – N/A
Labels and Labeling	G

N/A=not applicable for this review

*We do not typically search FAERS for label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We reviewed the proposed container labels, carton labeling, and Prescribing Information (PI) for Radicava (NDA 209176) for risk of medication error. The sponsor submitted the container labels and carton labeling with the June 16, 2016 submission and later submitted an updated PI and labels and labeling on September 13, 2016 and January 19, 2017, respectively. We identified the following areas of needed improvement which may contribute to medication errors:

- Section 2 Dosage and Administration and Section 3 Dosage Forms and Strengths in the PI use the prohibited abbreviation ‘IV’.
- Section 2.1 Dosage Information in the PI uses the terms “14 days” and (b) (4) to describe the dosing regimen. We recommend that one consistent term is used to mitigate the risk of confusion.

- Section 2.2 Administration Information in the PI includes uses a (b) (4) that may be misinterpreted and also lacks clarity regarding the infusion type, number of bags per dose and the infusion rate.
- Section 16 How Supplied/Storage and Handling in the PI includes the NDC number for the Radicava carton; however, the NDC number for the Radicava container is not provided. Additionally, the package configuration information should be revised to reflect that each carton contains two infusion bags.
- The carton labeling does not correctly display important product identifying information (e.g. dosage form, strength statement, and “Rx only” statements).
- The carton labeling contains infusion instructions that lack clarity.

We note that the review team has determined that the Medication Guide is not needed and should be revised to Patient Prescribing Information (PPI) format. We defer to the Division of Medical Policy Programs (DMPP) to provide recommendations for the PPI. We also note that the overwrap labeling for Radicava includes an oxygen indicator and labeling statements to inform users of the information conveyed by the oxygen indicator. We defer to the Office of Pharmaceutical Quality (OPQ) to provide recommendations regarding the oxygen indicator and the corresponding labeling statements.

4 CONCLUSION & RECOMMENDATIONS

We determined that there are areas within the Prescribing Information and carton labeling that can be improved upon to reduce the risk of medication errors and to increase clarity and prominence of key information. We find the container label acceptable from a medication error perspective. We provide recommendations below in Section 4.1 for the division and Section 4.2 for Mitsubishi Tanabe to address our concerns. We advise these recommendations are implemented prior to approval of this product.

4.1 RECOMMENDATIONS FOR THE DIVISION

A. Prescribing Information

1. Section 2 Dosage and Administration
 - i. The abbreviation “IV” appears multiple times in this section. We recommend all instances of “IV” are revised to “intravenous” to reflect the intended meaning and to mitigate the risk of misinterpretation.
2. Section 2 Dosage and Administration, 2.1 Dosage Information
 - i. The terms “14 days” and (b) (4) are both used in this section which may lead to confusion. Consider using one consistent term to mitigate the risk of confusion regarding the dosing schedule.
3. Section 2 Dosage and Administration, 2.2 Administration Information
 - i. Consider revising the statement (b) (4) to “RADICAVA is for intravenous infusion only”. We recommend

this revision to clarify the administration information and to minimize the risk of administering the drug as an intravenous bolus.

- ii. The administration instructions as presented lack clarity in the number of bags and the time required to complete the infusion. The administration information should be revised to clearly inform users that each 60 mg dose (two infusion bags) is infused over one hour. Therefore, we recommend that the sentences (b) (4)

(b) (4)
(b) (4)
(b) (4) are revised to “Administer each 60 mg dose of RADICAVA injection as two consecutive 30 mg infusion bags over 60 minutes (b) (4) (e.g. infusion rate approximately 1 mg per minute)”.

- iii. This section uses a (b) (4) and may lead to confusion and administration error. Delete the statement (b) (4)
(b) (4) We recommend this revision due to post-marketing reports (b) (4) may have the opposite of the intended meaning (b) (4)

4. Section 3 Dosage Forms and Strengths

- i. See recommendation A.1.i. and revise accordingly.

5. Section 16 How Supplied/Storage and Handling

- i. This section includes incorrect information regarding the number of bags supplied per carton. Revise the phrase (b) (4) to “2 bags per carton” to accurately reflect the carton package configuration for Radicava.
- ii. The NDC number for the carton labeling is included; however, the NDC number for the container label is not. Revise to include the NDC numbers for both package configurations.

4.2 RECOMMENDATIONS FOR THE MITSUBISHI TANABE

We recommend the following be implemented prior to approval of NDA 209176:

A. Carton labeling

- 1. Revise the strength statement to display the strength per total followed by strength per mL enclosed by parentheses, as depicted below.^b

30 mg/100 mL (0.3 mg/mL)

OR

30 mg/100 mL
(0.3 mg/mL)

^a Institute for Safe Medication Practices. (b) (4)

^b United States Pharmacopoeia (USP) General Chapter <7>

2. Delete the statement [REDACTED] (b) (4) and change to “Injection” to correctly display the dosage form.^c
3. Each dose of Radicava requires two infusion bags for a total infusion time of 60 minutes, and the carton labeling lists the infusion time as [REDACTED] (b) (4) minutes. This information may be misinterpreted [REDACTED] (b) (4). Therefore, the statement [REDACTED] (b) (4) should be revised to “Infuse each 30 mg/100 mL bag over a period of 30 minutes”
4. Relocate the “Rx Only” statement to the principal display panel (PDP) and ensure that it appears less prominent than other important information (e.g. proprietary name, established name, strength, route of administration) on the PDP.^d

^c USP General Chapter<1121> Nomenclature

^d Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2013. Available from <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf>.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Radicava that Mitsubishi Tanabe submitted on June 16, 2016 and September 13, 2016.

Table 2. Relevant Product Information for Radicava	
Initial Approval Date	N/A
Active Ingredient	Edaravone
Indication	Treatment of Amyotrophic Lateral Sclerosis (ALS)
Route of Administration	Intravenous infusion
Dosage Form	Injection Solution
Strength	30 mg/100 mL (0.3 mg/mL)
Dose and Frequency	60 mg administered intravenously over 60 minutes daily for 14 consecutive days followed by a 2-week drug free period (Cycle 1), and then administration of 60 mg administered intravenously over 60 minutes daily for 10 days within a 14 day period followed by a 2-week drug free period (Cycle 2 and thereafter).
How Supplied	30mg/100 mL sterile injection solution in polypropylene bag. Each carton will contain two infusion bags.
Storage	Store at up to 25°C (77°F). Excursions permitted from 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. Protect from light. Store in overwrapped package until time of use. Once the overwrap package is opened, use within 24 hours.

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On June 30, 2016, we searched the L:drive and AIMS using the term, edaravone, to identify reviews previously performed by DMEPA.

B.2 Results

Our search identified one previous proprietary name review^e, and we confirmed that our recommendation was considered.

^e Harris, Justine. Proprietary Name Review for Radicava (PIND 126396). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2016 MAY 9. RCM No.: 2016-2818367.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,^f along with postmarket medication error data, we reviewed the following Radicava labels and labeling submitted by Mitsubishi Tanabe on June 16, 2016 and later revised on September 13, 2016 and January 19, 2017 (see below).

- Container label (January 19, 2017)
- Carton labeling (January 19, 2017)
- Blister film/overwrap labeling (January 19, 2017)
- Prescribing Information (not pictured; September 13, 2016)
- Medication Guide (not pictured; September 13, 2016)

3 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

^f Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

EBONY A WHALEY
01/30/2017

LOLITA G WHITE
01/30/2017

**Interdisciplinary Review Team for QT Studies Consultation:
Thorough QT Study Review**

NDA	209176
Generic Name	Edaravone (MCI-186)
Sponsor	Mitsubishi Tanabe Pharma Corporation
Indication	Treatment of Amyotrophic Lateral Sclerosis (ALS)
Dosage Form	Injection
Drug Class	Free radical scavenger
Therapeutic Dosing Regimen	60 mg over 60 minutes IV daily for 14 consecutive days followed by a 2-week drug free period (Cycle 1), followed by 60 mg over 60 minutes IV daily for 10 days within a 14 day period followed by a 2-week drug free period (Cycle 2 and thereafter). In this study, 24-hour infusion of highest dose group of 0.2 mg/kg bolus + 0.5 mg/kg/h infusion reached a similar plasma concentration of edaravone (1164 ng/mL) with the estimated C _{max} after 60 mg/60 min IV infusion of edaravone.
Duration of Therapeutic Use	Chronic
Maximum Tolerated Dose	MDT has not been reached, highest dose administered is 0.2 mg/kg bolus + 0.5 mg/kg/h IV infusion for 24 hours
Submission Number and Date	6/16/2016 and 001
Review Division	DNP

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

1 SUMMARY

1.1 OVERALL SUMMARY OF FINDINGS

Due to the limitations of the study as noted below, MCI-186-E02 can not be used to exclude small effects (10 ms threshold) as per the ICH E14 and ICH E14 Q&A (R3) guidelines.

In this randomized, Phase I, double-blind, placebo-controlled, ascending IV dose study (MCI-186-E02), 46 subjects were enrolled and received following treatments:

- 0.1 mg/kg + 0.25 mg/kg/h infusion over 24 h (n=10),
- 0.2 mg/kg + 0.50 mg/kg/h infusion over 24 h (n=10),
- 0.05 mg/kg + 0.125 mg/kg/h infusion over 24 h (n=10), or

- placebo (n=16; pooled across cohorts).

The study did not evaluate directly the intended therapeutic dose (60 mg IV infusion in 60 min once daily). But, the 24-hour infusion of highest dose group of 0.2 mg/kg bolus + 0.5 mg/kg/h infusion in this study reached a similar end of infusion plasma concentration of edaravone (1164 ng/mL) as the estimated C_{max} after proposed therapeutic dosing of 60 mg/60 min IV infusion (C_{max} after 60 mg/60 min IV infusion of edaravone is estimated as 1049 ng/mL according to Population-PK simulations).

There are several limitations of this study which make it uninterpretable for excluding small QTc effects (<10 ms):

- There was no suprathreshold dose/exposure studied; therefore, the QTc effects at the high clinical exposure scenario have not been characterized. The primary route of elimination for the drug and its metabolites is renal route. Thus renal impairment likely constitutes the worst case high exposure scenario for the same therapeutic dose. There is no PK information available for quantifying this high exposure scenario and there was no suprathreshold dose studied to cover such exposures.

Note: The application states that the renal and hepatic impairment studies will be conducted in parallel with the NDA review.

- ECG quality and ECG/PK assessment is not adequate. Single 12-lead ECGs (no replicates) were measured at baseline pre-dose and at different time points. The matched ECG/PK sampling post end-of-infusion was not adequate to evaluate the possible hysteresis effect of concentration on response.
- ECG assay sensitivity was not established in the study. The study did not have any higher dose to evaluate effects at multiple-fold (at least 2-fold) of clinically relevant highest exposure to waive the requirement of a positive control as per ICH E14 Q&A (R3) guidance for early phase studies.

1.2 QT INTERDISCIPLINARY REVIEW TEAM'S COMMENTS

- We recommend that the sponsor conducts a TQT study for this product as a PMR to exclude small QT prolongation effects (10 ms threshold). The sponsor should submit the protocol for our review and comments.

2 PROPOSED LABEL

No labeling is proposed currently by the sponsor for QT effects. We recommend not to have any labeling language for QT effects based on this study.

3 BACKGROUND

3.1 PRODUCT INFORMATION

Edaravone is a compound with free radical scavenging effects and was developed by Mitsubishi Tanabe Pharma Corporation to be applied to various diseases in which free radicals are thought to be a mechanism of pathological processes. It is being considered for approval in the US for the treatment of amyotrophic lateral sclerosis (ALS) under orphan drug designation.

3.2 MARKET APPROVAL STATUS

Edaravone was approved for marketing in Japan since April 2001. The (b)(4) indication was for (b)(4) acute ischemic stroke. The number of patients having used the product in Japan as of March 31, 2014, estimated from the sales quantity of the product, is (b)(4) subjects, calculated as the minimum number of patients with assumption that all patients have been administered the product for 14 days. It recently got approval for the treatment of ALS in Japan in June 2015.

The sponsor intends to seek approval in US based on current data and establishing similarity between the Japanese and US ALS populations (refer to discussion of Question 1 in PIND 126396 meeting minutes, page 5, dated 01/07/2016 in DARRTS).

3.3 PRECLINICAL INFORMATION

Effects of edaravone on isolated cardiac tissues were investigated. A manual patch clamp study at body temperature in HEK293 transfected cells showed no effect (<5.0% inhibition) up to 100µM of edaravone on the hERG-mediated cardiac potassium ion current. From the results, at least a hundred-fold margin of safety compared to clinical settings of 60mg/60min is anticipated.

Edaravone did not affect respiratory function or the ECG at doses up to 100 mg/kg. However, in anesthetized dog at a dose of 30 mg/kg or more, transient decreases in mean blood pressure and increases in heart rate, carotid arterial blood flow, femoral arterial blood flow and cardiac output were observed. The maximum rate of change in left ventricular pressure was biphasic in which it transiently decreased and then increased. These changes were considered reflexive due to the presence of a reduction in arterial blood pressure and no direct effects up to 100 µM of edaravone on isolated cardiac tissues studies. There was no safety finding at 10 mg/kg in dogs.

The no observed adverse effect level (NOAEL) dose for repeated administration as bolus for 26 weeks from toxicology studies, was 10 mg/kg/day in rats, and 30 mg/kg in dogs.

Reviewer's comments: The cardiac safety report has noted following limitations for preclinical studies:

- *The preclinical general and safety pharmacology studies conducted for edaravone do not necessarily comply with the current regulatory standard of ICH S7A and S7B.*
- *These studies, although much more vast in scientific information, were not designated as GLP compliant.*
- *Additionally, the cardiovascular evaluation in the anesthetized state is not consistent with the standard use of conscious dogs. However, given the aggressive dosing used in the preclinical cardiovascular safety studies of 30 to 100 times the clinically relevant levels, there would not appear to be any concern of safety related to the findings.*

3.4 PREVIOUS CLINICAL EXPERIENCE

While electrocardiogram (ECG) was assessed in 5 healthy volunteer (HV) studies and a stroke study (MCI186-E04), no ECG waveform in an electric format is available in any study. No ECG was collected in ALS studies.

Study MCI186-E02 in HV was the only reliable study with adequate design and reliable conclusions (study reviewed in this submission). The other studies were not intended to define the ECG effects of treatment and, due to the very small numbers of subjects and high variability, no reliable conclusions were supported by the data. Amongst these, in the four HV studies ECG findings were inconclusive but showed no consistent trends suggesting QTc prolongation. ECG findings in one study of acute ischemic stroke were unreliable, due both to the very ill patient population studied, as well as based on unexpectedly large values for standard deviation of mean values of changes from Baseline in QTcB.

CV-related adverse events (AEs) were noted in 2.0% (2/100) of subjects receiving edaravone in HV studies, in 1.3% (11/817) in acute ischemic stroke (AIS) studies, in 3.3% (12/367) in subarachnoid hemorrhage (SAH) studies, and in 2.3% (8/349) in amyotrophic lateral sclerosis (ALS) studies. CV-related serious adverse events (SAEs) were noted in no subjects receiving edaravone in HV studies, in 0.4% (3/817) in AIS studies, in 0.3% (1/367) in SAH studies, and in 0.6% (2/349) in ALS studies.

There were no deaths in HV studies. There were 26 deaths (3.2%) in AIS studies, 27 deaths (7.3%) in SAH studies. There were 18 deaths (5.2%) in 5 ALS studies (MCI-186-12, -16, -17, -18 and -19). In no cases were the deaths attributed to treatment rather than to the underlying disease or complications of the disease. Of these, the only obviously cardiac-related death, a cardiac arrest in a subject in an ALS study, was deemed “unlikely related” to study drug by the investigator.

Pharmacovigilance activities showed that amongst the AEs or ADRs drug reactions reported spontaneously for commercially available edaravone in Japan, there were a total of 41 CV AEs and 34 ADRs (see Table 1 below). Serious AEs and ADRs for subjects with cerebral infarction included 1 patient with long QT syndrome and 2 patients with ventricular fibrillation and 2 patients with ventricular tachycardia. The report does not include AE/ADRs in ALS patients.

Table 1: Spontaneous Adverse Drug Reactions

Adverse Event (MedDRA ver.17.1) SOC PT	Cerebral Infarction			Others			Total
	Serious	Non-serious	Total	Serious	Non-serious	Total	
Cardiac disorders	27	6	33		1	1	34
Arrhythmia		1	1				1
Atrial fibrillation	3		3				3
Atrioventricular block complete	1		1				1
Bradycardia	2	1	3				3
Cardiac arrest	2		2				2
Cardiac failure	6	3	9				9
Cardiac failure acute	3		3				3
Cardiac failure congestive	3		3				3
Cyanosis	1		1				1
Long QT syndrome	1		1				1
Palpitations		1	1				1
Sinus arrest	1		1				1
Ventricular fibrillation	2		2				2
Ventricular tachycardia	2		2		1	1	3

Source: Table 45 in Cardiac Safety Review Report, page 64

3.5 CLINICAL PHARMACOLOGY

Appendix 6.1 summarizes the key features of edaravone's clinical pharmacology.

4 SPONSOR'S SUBMISSION

4.1 OVERVIEW

The QT-IRT reviewed the protocol prior to conducting this study under NDA 209176. The sponsor submitted the study report MCI-186-E02 for the study drug, including electronic datasets and waveforms to the ECG warehouse.

4.2 TQT STUDY

4.2.1 Title

A Phase I, double-blind, placebo-controlled, ascending dose clinical study investigating the pharmacokinetics, safety and tolerability of a bolus and subsequent infusion, of a new formulation of edaravone in male and female Caucasian subjects.

4.2.2 Protocol Number

MCI-186-E02

4.2.3 Study Dates

Date of first subject enrollment: 21 February 2006

Date of last subject follow-up: 18 July 2007

4.2.4 Objectives

Primary

- To assess the safety, tolerability and local tolerance of ascending single doses of edaravone in male and female Caucasian subjects.
- To determine the pharmacokinetic profiles of ascending single doses of edaravone in male and female Caucasian subjects.

Secondary

None

4.2.5 Study Description

4.2.5.1 Design

Phase I, double-blind, placebo-controlled, ascending dose clinical study.

4.2.5.2 Controls

Placebo control was used. Positive control (moxifloxacin) was not used.

4.2.5.3 Blinding

Treatment arms were blinded.

4.2.5.4 Treatment Arms

Study medication administration dose levels:

- Treatment group 1: 0.1 mg/kg bolus (3 min) + 0.25 mg/kg/h infusion over 23h57min.
- Treatment group 2: 0.2 mg/kg bolus (3 min) + 0.50 mg/kg/h infusion over 23h57min.
- Planned treatment group 3: 0.3 mg/kg bolus (3 min) + 0.75 mg/kg/h infusion over 23h57min.

As the observed plasma concentration of MCI-186 in group 2 was higher than the predicted profile, it was decided not to further dose escalate in group 3, but instead to lower the dose.

- Actual treatment group 3: 0.05 mg/kg bolus (3 min) + 0.125 mg/kg/h infusion over 23h57min.
- Reference treatment: Matching placebo: bolus (3 min) + infusion over 23h57min.

4.2.5.5 Sponsor's Justification for Doses

The table below (Table 2) summarises the dose-action relationships in monkeys and rats and the corresponding C_{ss} levels calculated from pharmacokinetic studies assuming that the doses and plasma concentrations are proportional at the given concentration range. Corresponding human doses are also shown in Table 2.

Table 2: Corresponding doses and free C_{ss} levels in humans, monkeys and rats

Human			Monkey [†]			Rat [†]			Estimated free C _{ss} (ng/mL)
Bolus (mg/kg)	+	Infusion (mg/kg/h)	Bolus (mg/kg)	+	Infusion (mg/kg/h)	Bolus (mg/kg)	+	Infusion (mg/kg/h)	
0.1	+	0.25	0.1	+	0.5 [‡]	0.2	+	1 ^{‡,§,}	30.22
0.2	+	0.5	0.2	+	1 ^{‡§}	0.4	+	2	60.44
0.3	+	0.75	0.3	+	1.5	0.6	+	3	90.66

* pMCAO model was used. Edaravone was administered 2h after the occlusion. Edaravone was infused over 22h following bolus administration.

† Intraluminal suture model, 2h ischaemia followed by reperfusion, was used. Edaravone treatment was commenced immediately after the reperfusion. Edaravone was infused over 24h following bolus administration.

‡ Doses that were actually administered in the dose-action relationship studies in animals

§ The doses that exhibited maximum effect in animals

|| The doses calculated from pharmacokinetic studies and considered to give the same C_{ss} level.

Source: Table 2 in CSR for study MCI-186-E02, page 38

The most effective dose in rat models was 1 mg/kg/h (C_{ss} = 30.22 ng/mL). In monkey studies, the efficacy at “0.2 mg/kg + 1 mg/kg/h” and “0.4 mg/kg/h + 2 mg/kg/h” were equally effective, i.e. the efficacy reached plateau at “0.2 mg/kg + 1 mg/kg/h”.

It was considered appropriate to study the efficacy of edaravone in humans at doses that would achieve similar free plasma concentrations to those associated with the most effective doses in animal model studies, namely free C_{ss} levels of 30.22–60.44 ng/mL. It was estimated that these plasma levels would be achieved by doses of 0.25 and 0.5 mg/kg/h respectively, in humans, and therefore these doses, and one dose above them, were chosen for evaluation in this Phase I volunteer study. After group 2 it was decided not to dose escalate but to lower the dose since the PK profiles in group 1 and 2 were higher than the predicted profiles.

In order to optimise the safety of patients in future clinical trials, safety margins in relation to the neurotoxic findings were calculated for each of the proposed doses, based on the toxicokinetic data from the recent non-clinical studies. These are presented in Table 3.

The free AUC_{total} at NOAEL (120 mg/kg/d) in the 5-day treatment with 28-day withdrawal study was 41.9 µg·h/mL. The Safety Margin based on this parameter was estimated to be approximately 57.7, 28.9, and 19.2 for the 0.25, 0.5, and 0.75 mg/kg/h doses (given over 24 hours), respectively.

The free C_{ss} at NOAEL (120 mg/kg/d) in the 5-day treatment with 28-day withdrawal study was 0.39 µg/mL (390 ng/mL). The Safety Margin based on this parameter is estimated to be approximately 12.9, 6.5, and 4.3 for the 0.25, 0.5, and 0.75 mg/kg/h doses (given over 24h) respectively.

Therefore, in relation to the neurotoxic findings the safety margins at the intended doses and duration of treatment were considered sufficient.

Table 3: Doses and estimated safety margins in relation to neurotoxic findings

	Dose	C _{ss} (µg/ml)		AUC _{24h} (µg•h/ml)		AUC _{total} (µg•h/ml)	
		Female [†]	SM	Male [†]	SM	Male [†]	SM
NOAEL*	120mg/kg/day * 5 days	0.75 (0.39)	-	16.1 (8.37)	-	80.5 (41.9)	-
Group 1	0.1 mg/kg bolus dose + 0.25 mg/kg/h * 24h	0.37 (0.03)	2.0 (12.9)	8.95 (0.73)	1.8 (11.5)	8.95 (0.73)	9.0 (57.7)
Group 2	0.2 mg/kg bolus dose + 0.5 mg/kg/h * 24h	0.75 (0.06)	1.0 (6.5)	17.9 (1.45)	0.9 (5.8)	17.9 (1.45)	4.5 (28.9)
Group 3	0.3 mg/kg bolus dose + 0.75 mg/kg/h * 24h	1.12 (0.09)	0.7 (4.3)	26.9 (2.18)	0.6 (3.8)	26.9 (2.18)	3.0 (19.2)

* 5-day treatment and 4-week withdrawal in dog

† Lower values in both sexes were applied.

Figures in parentheses are free fraction values calculated assuming that the protein binding rates in dogs and humans are 48.0% and 91.9% respectively.

SM = Safety Margin

Source: Table 3 in CSR for study MCI-186-E02, page 39

In addition, the safety margins in relation to non-neurotoxic findings at the intended doses and duration of treatment were considered sufficient for both the infusion doses and each of the bolus doses (the latter being > 25 for all 3 doses).

Patients who suffer an acute ischaemic stroke have a limited amount of time before brain tissue dies (“time is brain”). Therefore, therapeutic intervention needs to be implemented at the earliest opportunity. A rapid bolus dose was selected for this study in order to achieve the anticipated effective plasma concentrations as soon as possible. This dosing strategy is likely to optimise the anticipated efficacy of edaravone.

Reviewer’s Comment: In this study, 24-hour infusion of highest dose group of 0.2 mg/kg bolus + 0.5 mg/kg/h infusion reached a similar plasma concentration of edaravone (1164 ng/mL) with the estimated C_{max} after 60 mg/60 min IV infusion (proposed therapeutic dosing). There is no suprathreshold dose/exposures studied in this study. The primary route of elimination for the drug and its metabolites is renal route. Thus renal impairment likely constitutes the worst case high exposure scenario. There is no PK information available for this high exposure scenario. The application states that the renal and hepatic impairment studies will be conducted in parallel with the NDA review.

4.2.5.6 Instructions with Regard to Meals

Reviewer’s Comment: Not applicable, since the dosing is intravenous administration.

4.2.5.7 ECG and PK Assessments

ECG: Screening, Day -1, Day 1 (pre-dose, 30 min, and 1, 2, 4, 8, 12, 16, 20, 24, 30, 36, 42 and 48 h after the start of the infusion) and 1 week follow-up visit

PK: Pre-dose, and at following time points after the start of infusion- 7 min, 15 min, 30 min, and 1 h, 2 h, 4 h, 8 h, 12 h, 24 h, 24 h 10 min, 24 h 20 min, 24 h 30 min, 25 h, 26 h, 27 h, 29 h, 31 h, 33 h, 48 h

Reviewer's Comment: Acceptable. T_{max} is approximately at the end of infusion. Sampling is appropriate to cover T_{max} and any delayed effects upto 24 hour after the end of dosing (infusion). Only time matched ECG and PK samples are utilized for the analysis in the reviewer's analysis.

4.2.5.8 Baseline

The sponsor used pre-dose QTc at Day 0 as baselines.

4.2.6 ECG Collection

A 12-Lead ECG was recorded at screening, Day -1, Day 1 (pre-dose, 30 min, 1h, 2h, 4h, 8h, 12h, 16h, 20h, 24h, 30h, 36h, 42h and 48h after start of the infusion) and at the one (1) week follow-up visit.

4.2.7 Sponsor's Results

4.2.7.1 Study Subjects

Forty-six eligible subjects were randomly assigned and completed to one of the three groups. No subjects were withdrawn from the study after dosing or after completion. Four (4) subjects were replaced because of protocol violation due to infusion failure (two (2) in group 1 and two (2) in group 3).

For PK analysis, only the subjects who completed the study as per protocol were included (N=42). All subjects (including the 4 subjects who were replaced) were included in the safety analyses (46 subjects).

4.2.7.2 Statistical Analyses

4.2.7.2.1 Primary Analysis

Not provided.

Reviewer's Comments: We will provide our independent analysis result in Section 5.2.

4.2.7.2.2 Assay Sensitivity

No assay sensitivity analysis is performed.

4.2.7.2.3 Categorical Analysis

Not Provided.

4.2.7.2.4 Additional Analyses

4.2.7.3 Safety Analysis

Safety analysis showed that MCI-186 at all doses tested was safe and well tolerated. There were no clinically significant changes in QST or neurological examination.

4.2.7.4 Clinical Pharmacology

4.2.7.4.1 Pharmacokinetic Analysis

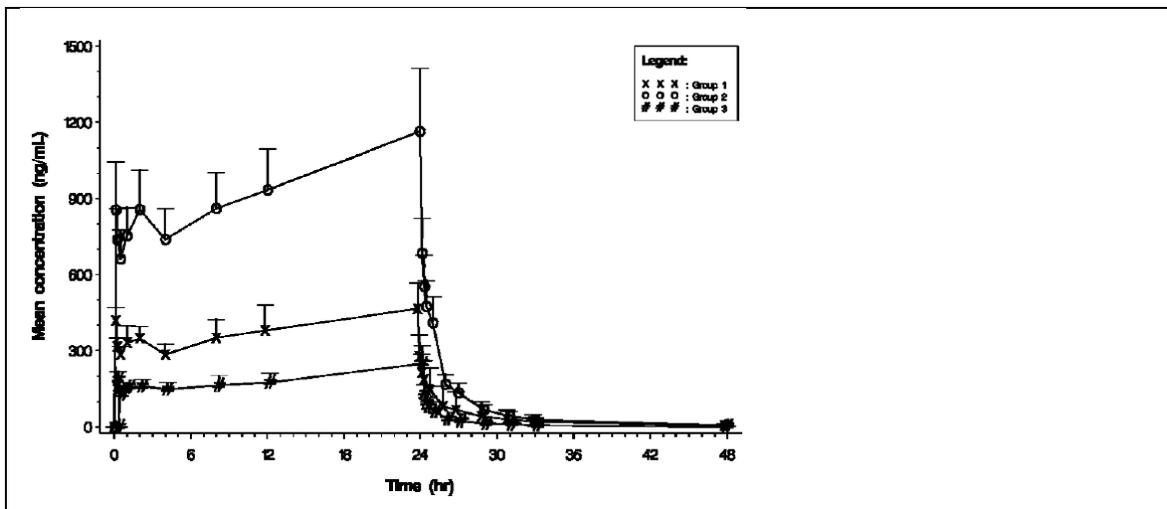
The PK results are presented in Table 4 and the PK profiles are shown in Figure 1. In this study, 24-hour infusion of highest dose group of 0.2 mg/kg bolus + 0.5 mg/kg/h infusion reached a similar plasma concentration of edaravone as the estimated C_{max} after 60 mg/60 min IV infusion (proposed therapeutic dosing). There is no suprathreshold dose/exposures studied in this study.

Table 4: Pharmacokinetic parameters for MCI-186 (edaravone) and its metabolites MCI-186 glucuronide and MCI-186 sulfate in plasma after bolus+continuous IV infusion dosing

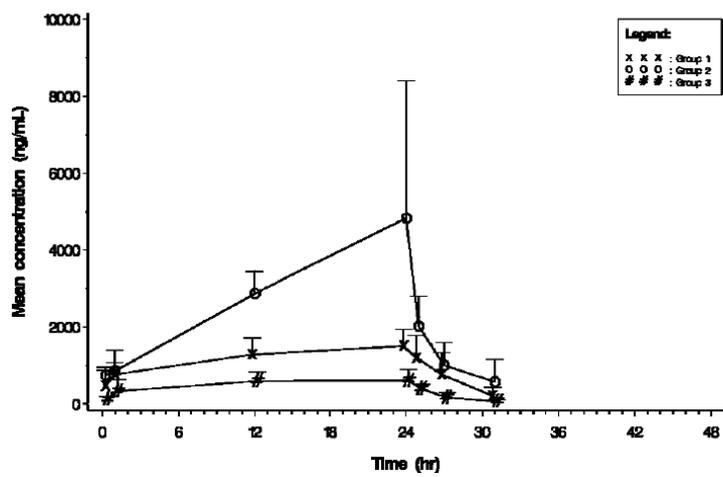
Species	Treatment	GeoMean C_{max} (ng/mL)	GeoMean AUC_{0-inf} (ng*h/mL)
MCI-186	0.1 mg/kg+0.25 mg/kg over 24 hours	472.9	9725.1
	0.2 mg/kg+0.50 mg/kg over 24 hours	1140.6	23805.4
	0.05 mg/kg+0.125 mg/kg over 24 hours	242.5	4680.3
MCI-186 glucuronide	0.1 mg/kg+0.25 mg/kg over 24 hours	1734.4	34330.6
	0.2 mg/kg+0.50 mg/kg over 24 hours	4549.9	74132.8
	0.05 mg/kg+0.125 mg/kg over 24 hours	684.9	13437.6
MCI-186 sulfate	0.1 mg/kg+0.25 mg/kg over 24 hours	4437.2	98082
	0.2 mg/kg+0.50 mg/kg over 24 hours	10489.3	222385
	0.05 mg/kg+0.125 mg/kg over 24 hours	2277.3	49528.7

Figure 1: Arithmetic mean (+ SD) concentration-versus-time curves for MCI-186 unchanged form (panel A), MCI-186 glucuronide metabolite (panel B), MCI-186 sulfate metabolite (panel C); PK population, group 1 (0.1 mg/kg + 0.25 mg/kg/h), group 2 (0.2 mg/kg + 0.50 mg/kg/h) and group 3 (0.05 mg/kg + 0.125 mg/kg/h); N=10

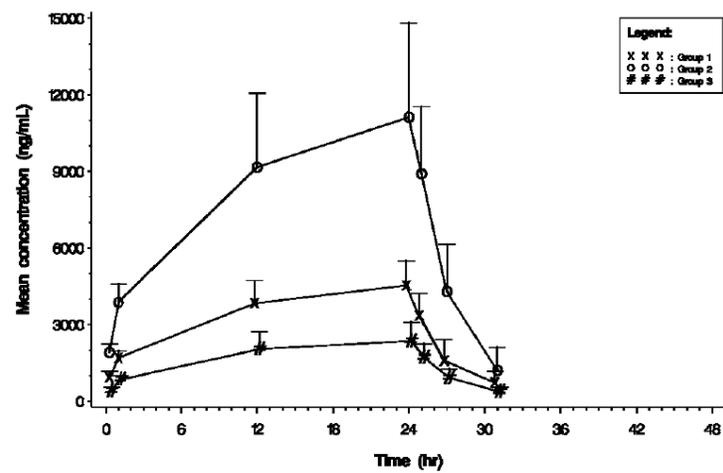
A.



B.



C.



4.2.7.4.2 Exposure-Response Analysis

No exposure-response analyses were carried out by the sponsor.

Reviewer's Analysis: A plot of $\Delta\Delta QTcF$ vs. edaravone concentrations is presented in Figure 5. No metabolite concentrations are provided.

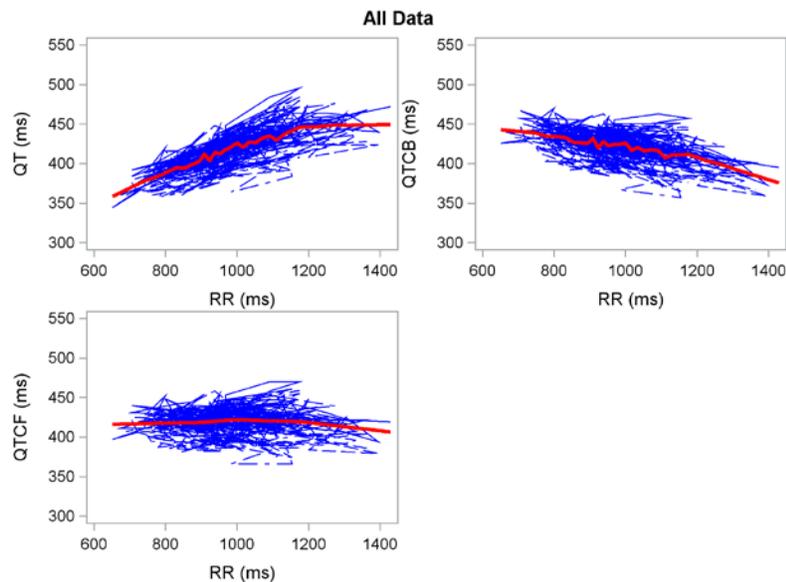
5 REVIEWERS' ASSESSMENT

5.1 EVALUATION OF THE QT/RR CORRECTION METHOD

This review did not evaluate of the QT/RR correction method because the sponsor only provided QTcB and QTcF correction intervals. This reviewer chooses to present QTcF for the primary statistical analysis.

The relationship between different correction methods and RR is presented in Figure 2.

Figure 2: QT, QTcB, and QTcF vs. RR (Each Subject's Data Points are Connected with a Line)



5.2 STATISTICAL ASSESSMENTS

5.2.1 QTc Analysis

5.2.1.1 The Primary Analysis for the Study Drug

The statistical reviewer used mixed model to analyze the $\Delta QTcF$ effect. The model includes treatments as fixed effect and baseline values as covariate. Three treatment groups: group 1: 0.1 mg/kg bolus (3 min) + 0.25 mg/kg/h infusion over 23 h 57 min; group 2: 0.2 mg/kg bolus (3 min) + 0.50 mg/kg/h infusion over 23 h 57 min and group 3: 0.3 mg/kg bolus (3 min) + 0.75 mg/kg/h infusion over 23 h 57 min. The analysis results are listed in Table 5. The largest upper bounds of the 2 sided 90% CI for

the mean differences between group 1 and placebo, between group 2 and placebo, and between group 3 and placebo are 14.0 ms, 12.4 ms, and 11.2 ms, respectively.

Table 5: Analysis Results of Δ QTcF and $\Delta\Delta$ QTcF for Edaravone Continuous IV Dose (Study MCI-186-E02)

		Treatment Group											
		Group 3 0.05 mg/kg+0.125 mg/kg x 24 h				Group 1 0.1 mg/kg+0.25 mg/kg x 24 h				Group 2 0.2 mg/kg+0.50 mg/kg x 24 h			
		Δ QTcF		$\Delta\Delta$ QTcF		Δ QTcF		$\Delta\Delta$ QTcF		Δ QTcF		$\Delta\Delta$ QTcF	
Time (h)	LS Mean	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI
0.5	-4.0	10	-4.1	-0.1	(-6.3, 6.2)	10	-5.0	-1.0	(-7.3, 5.3)	10	-3.2	0.9	(-5.4, 7.2)
1	0.2	10	-2.6	-2.8	(-9.0, 3.4)	10	-3.1	-3.3	(-9.5, 2.9)	10	1.3	1.1	(-5.1, 7.3)
2	-2.6	10	-0.3	2.3	(-4.7, 9.4)	10	-0.1	2.5	(-4.5, 9.5)	10	3.3	5.9	(-1.2, 12.9)
4	-5.5	10	-12.0	-6.5	(-12.8, -0.1)	10	-4.6	0.9	(-5.4, 7.3)	10	-11.2	-5.7	(-12.1, 0.7)
8	-6.4	10	-12.1	-5.7	(-12.0, 0.6)	10	-5.1	1.3	(-5.0, 7.6)	10	-7.7	-1.3	(-7.6, 4.9)
12	-4.3	10	-5.5	-1.2	(-8.9, 6.5)	10	-5.8	-1.5	(-9.2, 6.2)	10	-1.3	3.0	(-4.7, 10.8)
16	2.6	10	3.6	1.1	(-9.1, 11.2)	10	2.2	-0.4	(-10.6, 9.8)	10	-3.7	-6.3	(-16.5, 3.9)
20	3.7	10	4.7	1.0	(-7.3, 9.4)	10	-0.4	-4.1	(-12.5, 4.2)	10	-6.6	-10.3	(-18.7, -1.9)
24	-1.6	10	-6.4	-4.8	(-14.5, 4.9)	10	2.0	3.6	(-6.1, 13.3)	10	-3.3	-1.7	(-11.4, 8.0)
30	-11.7	10	-13.3	-1.6	(-9.5, 6.4)	10	-5.7	6.0	(-1.9, 14.0)	10	-7.3	4.5	(-3.5, 12.4)
36	-2.1	10	-13.2	-11.2	(-19.6, -2.7)	10	-11.4	-9.4	(-17.8, -0.9)	10	-8.2	-6.1	(-14.6, 2.3)
42	-1.1	10	0.5	1.6	(-6.5, 9.6)	10	4.8	5.9	(-2.1, 14.0)	10	2.2	3.3	(-4.8, 11.3)
48	-3.4	10	-6.9	-3.5	(-10.4, 3.4)	10	-2.4	1.0	(-5.9, 7.8)	10	-6.6	-3.2	(-10.1, 3.7)

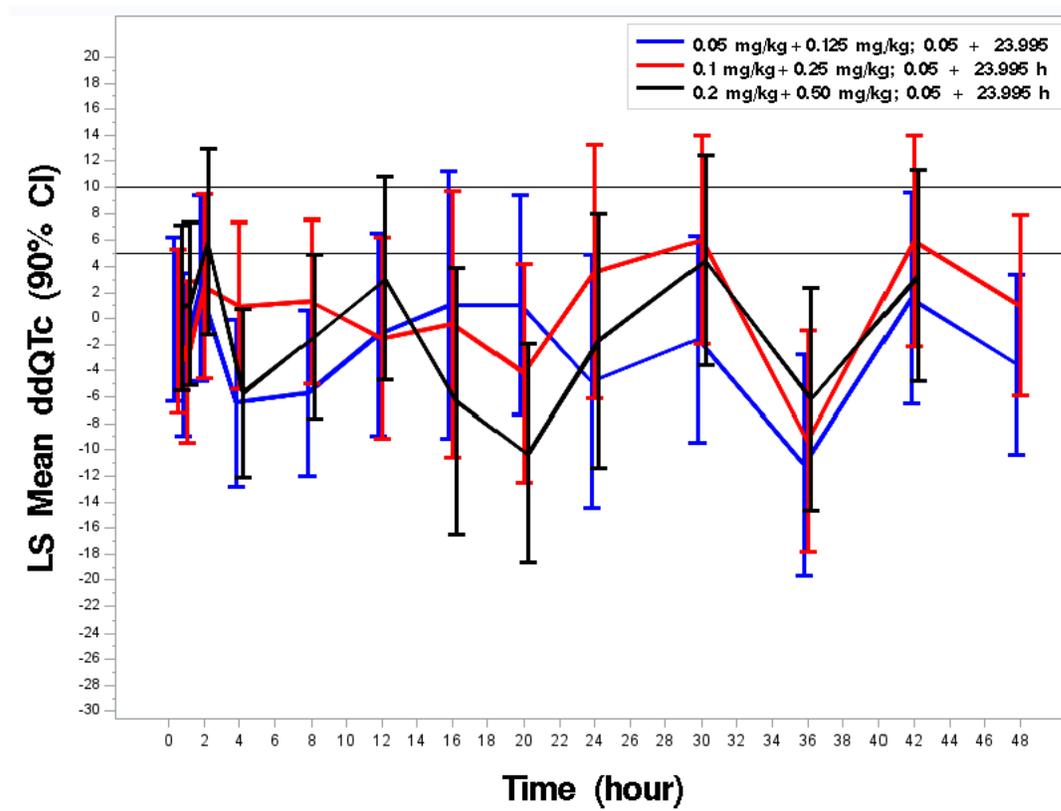
5.2.1.2 Assay Sensitivity Analysis

No assay sensitivity analysis is performed in this study because no positive control arm was included.

5.2.1.3 Graph of $\Delta\Delta$ QTcF Over Time

The following figure displays the time profile of $\Delta\Delta$ QTcF for different treatment groups.

Figure 3: Mean and 90% CI $\Delta\Delta$ QTcF Timecourse



5.2.1.4 Categorical Analysis

Table 6 lists the number of subjects as well as the number of observations whose QTcF values are ≤ 450 ms, between 450 ms and 480 ms, between 480 and 500, and over 500 ms. No subject's QTcF is above 480 ms.

Table 6: Categorical Analysis for QTcF

Treatment Group	Total N	Value ≤ 450 ms	450 ms < Value ≤ 480 ms	480 ms < Value ≤ 500 ms	Value > 500
0.05 mg/kg+0.125 mg/kg ; 0.05 + 23.995	10	10 (100%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
0.1 mg/kg+0.25 mg/kg; 0.05 + 23.995 h	10	8 (80.0%)	2 (20.0%)	0 (0.0%)	0 (0.0%)
0.2 mg/kg+0.50 mg/kg; 0.05 + 23.995 h	10	9 (90.0%)	1 (10.0%)	0 (0.0%)	0 (0.0%)
Placebo	16	13 (81.3%)	3 (18.8%)	0 (0.0%)	0 (0.0%)

Table 7 lists the categorical analysis results for Δ QTcF. No subject's change from baseline is above 60 ms.

Table 7: Categorical Analysis of Δ QTcF

Treatment Group	Total N	Value \leq 30 ms	30 ms<Value \leq 60 ms	60 ms<Value \leq 90 ms	Value>90 ms
0.05 mg/kg+0.125 mg/kg; 0.05 + 23.995	10	10 (100%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
0.1 mg/kg+0.25 mg/kg; 0.05 + 23.995 h	10	9 (90.0%)	1 (10.0%)	0 (0.0%)	0 (0.0%)
0.2 mg/kg+0.50 mg/kg; 0.05 + 23.995 h	10	10 (100%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Placebo	16	14 (87.5%)	2 (12.5%)	0 (0.0%)	0 (0.0%)

5.2.2 HR Analysis

The statistical reviewer used the same mixed model to analyze the Δ HR effect. The model includes treatments as fixed effect and baseline values as covariate. Three treatment groups: group 1: 0.1 mg/kg bolus (3 min) + 0.25 mg/kg/h infusion over 23 h 57 min; group 2: 0.2 mg/kg bolus (3 min) + 0.50 mg/kg/h infusion over 23 h 57 min and group 3: 0.3 mg/kg bolus (3 min) + 0.75 mg/kg/h infusion over 23 h 57 min. The analysis results are listed in Table 8. The largest upper bounds of the 2 sided 90% CI for the mean differences between group 1 and placebo, and between group 2 and placebo, and between group 3 and placebo are 6.6 bmp, 5.8 bmp and 5.7 bmp, respectively. Table 9 presents the categorical analysis of HR. No subject who experienced HR interval greater than 100 bmp is in Edaravone group.

Table 8: Analysis Results of Δ HR and $\Delta\Delta$ HR for Edaravone Continuous IV Dose

Time (h)	Treatment Group												
	Placebo	0.05 mg/kg+0.125 mg/kg; 0.05 + 23.995				0.1 mg/kg+0.25 mg/kg; 0.05 + 23.995 h				0.2 mg/kg+0.50 mg/kg; 0.05 + 23.995 h			
	Δ HR	Δ HR		$\Delta\Delta$ HR		Δ HR		$\Delta\Delta$ HR		Δ HR		$\Delta\Delta$ HR	
LS Mean	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI	
0.5	-2.3	10	-3.4	-1.1	(-3.7, 1.4)	10	-3.7	-1.5	(-4.0, 1.1)	10	-1.3	0.9	(-1.6, 3.5)
1	-2.6	10	-4.4	-1.8	(-4.3, 0.6)	10	-4.8	-2.1	(-4.6, 0.3)	10	-2.0	0.7	(-1.8, 3.1)
2	-3.5	10	-3.9	-0.3	(-3.2, 2.6)	10	-3.7	-0.2	(-3.1, 2.7)	10	-1.6	1.9	(-0.9, 4.8)
4	4.4	10	4.2	-0.1	(-4.1, 3.8)	10	6.9	2.6	(-1.4, 6.6)	10	5.0	0.7	(-3.3, 4.6)
8	1.0	10	1.1	0.1	(-3.8, 4.0)	10	-0.5	-1.5	(-5.4, 2.4)	10	1.6	0.6	(-3.2, 4.4)
12	2.9	10	1.6	-1.3	(-5.0, 2.5)	10	3.1	0.2	(-3.5, 4.0)	10	2.3	-0.6	(-4.3, 3.1)
16	-0.2	10	-1.7	-1.4	(-6.3, 3.4)	10	-4.5	-4.3	(-9.1, 0.5)	10	0.8	1.0	(-3.8, 5.8)
20	-0.8	10	0.3	1.1	(-3.6, 5.7)	10	-2.4	-1.6	(-6.3, 3.1)	10	-2.5	-1.7	(-6.4, 2.9)
24	0.4	10	-3.3	-3.7	(-7.5, 0.2)	10	-1.0	-1.4	(-5.2, 2.4)	10	0.7	0.3	(-3.5, 4.1)
30	0.8	10	0.4	-0.3	(-4.3, 3.7)	10	-2.6	-3.4	(-7.4, 0.6)	10	0.6	-0.2	(-4.2, 3.8)
36	5.4	10	3.2	-2.1	(-6.5, 2.3)	10	1.4	-4.0	(-8.4, 0.5)	10	1.2	-4.2	(-8.6, 0.2)
42	-0.4	10	-0.1	0.3	(-3.6, 4.2)	10	-2.5	-2.2	(-6.1, 1.8)	10	-1.2	-0.9	(-4.8, 3.0)
48	1.0	10	-0.5	-1.5	(-4.7, 1.8)	10	-0.1	-1.2	(-4.4, 2.1)	10	1.2	0.2	(-3.1, 3.4)

Table 9: Categorical Analysis for HR

Treatment Group	Total N	HR ≤ 100 bmp	HR >100 bmp
0.05 mg/kg+0.125 mg/kg; 0.05 + 23.995	10	10 (100%)	0 (0.0%)
0.1 mg/kg+0.25 mg/kg; 0.05 + 23.995 h	10	10 (100%)	0 (0.0%)
0.2 mg/kg+0.50 mg/kg; 0.05 + 23.995 h	10	10 (100%)	0 (0.0%)
Placebo	16	16 (100%)	0 (0.0%)

5.2.3 PR Analysis

The statistical reviewer used the same mixed model to analyze the Δ PR effect. The model includes treatments as fixed effect and baseline values as covariate. Three treatment groups: treatment group 1: 0.1 mg/kg bolus (3 min) + 0.25 mg/kg/h infusion over 23 h 57 min; treatment group 2: 0.2 mg/kg bolus (3 min) + 0.50 mg/kg/h infusion over 23 h 57 min and treatment group 3: 0.3 mg/kg bolus (3 min) + 0.75 mg/kg/h infusion over 23 h 57 min. The analysis results are listed in Table 10. The largest upper bounds of the 2 sided 90% CI for the mean differences between treatment group 1 and placebo, and between treatment group 2 and placebo, and between treatment group 3 and placebo are 12.8 ms, 12.4 ms and 12.8 ms, respectively. Table 11 presents the categorical analysis of PR. Six subject who experienced PR interval greater than 200 ms are in Edaravone group.

Table 10: Analysis Results of Δ PR and $\Delta\Delta$ PR for Edaravone Continuous IV Dose (Study MCI-186-E02)

		Treatment Group											
		0.05 mg/kg+0.125 mg/kg; 0.05 + 23.995				0.1 mg/kg+0.25 mg/kg; 0.05 + 23.995 h				0.2 mg/kg+0.50 mg/kg; 0.05 + 23.995 h			
		Δ PR		$\Delta\Delta$ PR		Δ PR		$\Delta\Delta$ PR		Δ PR		$\Delta\Delta$ PR	
Time (h)	LS Mean	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI
0.5	-1.0	10	-0.7	0.3	(-6.9, 7.4)	10	0.8	1.8	(-5.2, 8.8)	10	0.3	1.3	(-5.9, 8.5)
1	2.5	10	0.7	-1.8	(-8.2, 4.6)	10	1.4	-1.2	(-7.5, 5.1)	10	5.8	3.2	(-3.2, 9.7)
2	0.7	10	2.1	1.4	(-4.7, 7.5)	10	2.5	1.7	(-4.2, 7.7)	10	5.0	4.3	(-1.8, 10.4)
4	-3.1	10	-0.7	2.4	(-4.6, 9.4)	10	-5.1	-2.0	(-8.8, 4.9)	10	-1.1	2.0	(-5.0, 9.0)
8	-3.0	10	-3.5	-0.4	(-7.4, 6.5)	10	-1.0	2.0	(-4.8, 8.9)	10	-4.6	-1.6	(-8.6, 5.4)
12	-3.9	10	-5.1	-1.3	(-8.1, 5.5)	10	1.2	5.0	(-1.6, 11.7)	10	-0.7	3.2	(-3.7, 10.1)
16	3.5	10	3.6	0.1	(-6.4, 6.5)	10	4.0	0.4	(-5.9, 6.8)	10	2.8	-0.7	(-7.2, 5.8)
20	4.3	10	3.6	-0.7	(-9.0, 7.7)	10	6.6	2.3	(-5.9, 10.5)	10	6.1	1.8	(-6.6, 10.2)

		Treatment Group											
		0.05 mg/kg+0.125 mg/kg; 0.05 + 23.995				0.1 mg/kg+0.25 mg/kg; 0.05 + 23.995 h				0.2 mg/kg+0.50 mg/kg; 0.05 + 23.995 h			
		ΔPR		ΔΔPR		ΔPR		ΔΔPR		ΔPR		ΔΔPR	
Time (h)	LS Mean	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI
24	-1.8	10	0.2	2.0	(-4.7, 8.8)	10	-2.6	-0.7	(-7.3, 5.9)	10	-5.6	-3.8	(-10.5, 3.0)
30	-1.7	10	-0.7	1.1	(-6.0, 8.1)	10	-1.2	0.6	(-6.4, 7.5)	10	-2.1	-0.4	(-7.5, 6.7)
36	-3.5	10	-2.7	0.9	(-5.1, 6.8)	10	-0.7	2.8	(-3.1, 8.6)	10	-2.6	0.9	(-5.0, 6.9)
42	1.1	10	6.0	4.9	(-3.0, 12.8)	10	6.2	5.1	(-2.7, 12.8)	10	1.3	0.2	(-7.7, 8.1)
48	-6.3	10	-0.5	5.8	(0.1, 11.5)	10	-0.6	5.7	(0.1, 11.2)	10	0.4	6.7	(1.0, 12.4)

Table 11: Categorical Analysis for PR

Treatment Group	Total N	PR ≤ 200 ms	PR >200 ms
0.05 mg/kg+0.125 mg/kg; 0.05 + 23.995	10	6 (60.0%)	4 (40.0%)
0.1 mg/kg+0.25 mg/kg; 0.05 + 23.995 h	10	9 (90.0%)	1 (10.0%)
0.2 mg/kg+0.50 mg/kg; 0.05 + 23.995 h	10	9 (90.0%)	1 (10.0%)
Placebo	16	14 (87.5%)	2 (12.5%)

5.2.4 QRS Analysis

The statistical reviewer used the same mixed model to analyze the ΔQRS effect. The model includes treatments as fixed effect and baseline values as covariate. Three treatment groups: group 1: 0.1 mg/kg bolus (3 min) + 0.25 mg/kg/h infusion over 23 h 57 min; group 2: 0.2 mg/kg bolus (3 min) + 0.50 mg/kg/h infusion over 23 h 57 min and group 3: 0.3 mg/kg bolus (3 min) + 0.75 mg/kg/h infusion over 23 h 57 min. The analysis results are listed in Table 12. The largest upper bounds of the 2 sided 90% CI for the mean differences between group 1 and placebo, and between group 2 and placebo, and between group 3 and placebo are 4.3 ms, 2.4 ms and 4.4 ms, respectively. Table 13 presents the categorical analysis of QRS. No subject who experienced QRS interval greater than 110 ms is in Edaravone group.

Table 12: Analysis Results of ΔQRS and ΔΔQRS Edaravone Continuous IV Dose (Study MCI-186-E02)

Treatment Group	
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	Placebo	0.05 mg/kg+0.125 mg/kg; 0.05 + 23.995				0.1 mg/kg+0.25 mg/kg; 0.05 + 23.995 h				0.2 mg/kg+0.50 mg/kg; 0.05 + 23.995 h			
	ΔQRS	ΔQRS		ΔΔQRS		ΔQRS		ΔΔQRS		ΔQRS		ΔΔQRS	
Time (h)	LS Mean	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI
0.5	-0.7	10	-1.0	-0.3	(-2.9, 2.3)	10	-0.5	0.1	(-2.5, 2.7)	10	-2.7	-2.0	(-4.6, 0.6)
1	-1.7	10	-0.1	1.5	(-1.3, 4.4)	10	-0.9	0.7	(-2.1, 3.6)	10	-3.9	-2.2	(-5.0, 0.7)
2	-1.6	10	-0.7	0.9	(-2.0, 3.7)	10	-2.6	-1.0	(-3.8, 1.9)	10	-3.0	-1.4	(-4.2, 1.5)
4	0.4	10	-1.0	-1.4	(-4.9, 2.2)	10	-0.5	-0.8	(-4.4, 2.7)	10	-3.3	-3.7	(-7.3, -0.1)
8	-1.9	10	-2.4	-0.4	(-3.0, 2.2)	10	-0.3	1.7	(-0.9, 4.3)	10	-4.0	-2.1	(-4.7, 0.5)
12	-0.4	10	-1.4	-1.0	(-4.0, 1.9)	10	-1.3	-0.9	(-3.8, 2.0)	10	-2.9	-2.6	(-5.5, 0.4)
16	-0.5	10	-0.4	0.1	(-2.6, 2.8)	10	0.1	0.5	(-2.2, 3.2)	10	-1.4	-1.0	(-3.7, 1.7)
20	-0.4	10	-1.0	-0.6	(-3.2, 2.0)	10	-2.2	-1.8	(-4.4, 0.8)	10	-1.5	-1.1	(-3.7, 1.5)
24	-1.4	10	-0.8	0.6	(-2.2, 3.4)	10	0.0	1.4	(-1.4, 4.2)	10	-2.8	-1.4	(-4.2, 1.4)
30	-2.5	10	-2.0	0.5	(-2.7, 3.6)	10	-2.4	0.0	(-3.2, 3.2)	10	-3.3	-0.8	(-4.0, 2.4)
36	-0.1	10	-1.4	-1.3	(-5.3, 2.6)	10	-1.9	-1.8	(-5.7, 2.1)	10	-2.9	-2.8	(-6.7, 1.2)
42	0.6	10	-1.2	-1.8	(-5.7, 2.1)	10	-0.8	-1.4	(-5.4, 2.5)	10	-2.3	-2.9	(-6.8, 1.0)
48	-0.2	10	-0.5	-0.3	(-3.6, 3.0)	10	-1.0	-0.8	(-4.1, 2.5)	10	-4.4	-4.2	(-7.5, -0.9)

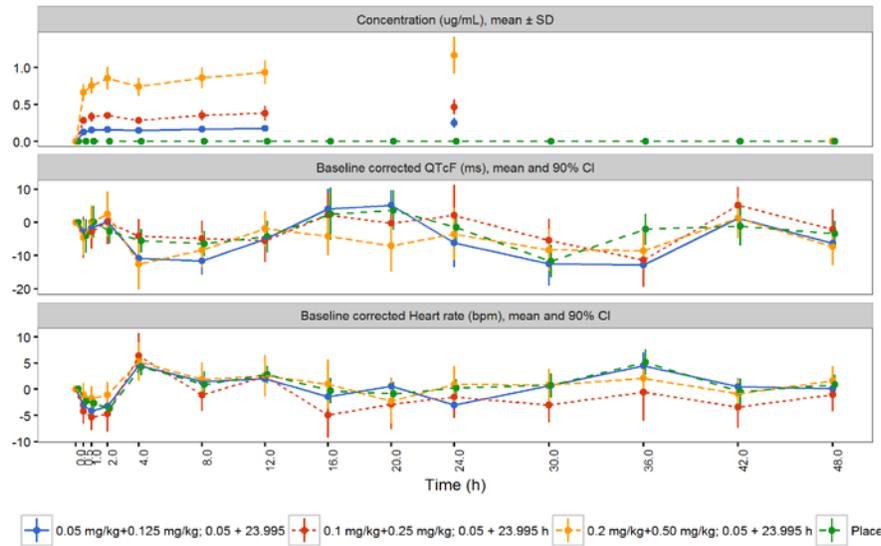
Table 13: Categorical Analysis for QRS

Treatment Group	Total N	QRS ≤ 110 ms	QRS > 110 ms
0.05 mg/kg+0.125 mg/kg; 0.05 + 23.995h	10	10 (100%)	0 (0.0%)
0.1 mg/kg+0.25 mg/kg; 0.05 + 23.995 h	10	10 (100%)	0 (0.0%)
0.2 mg/kg+0.50 mg/kg; 0.05 + 23.995 h	10	10 (100%)	0 (0.0%)
Placebo	16	16 (100%)	0 (0.0%)

5.3 CLINICAL PHARMACOLOGY ASSESSMENTS

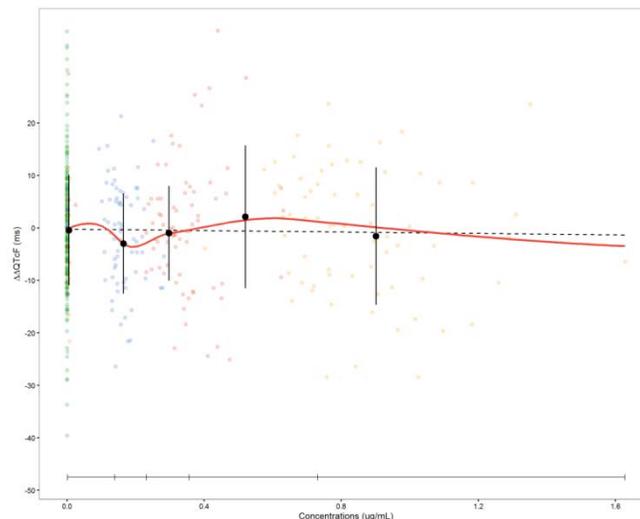
The mean concentration-time profiles for drug and metabolites are illustrated in Figure 1. Figure 4 shows a comparison of time profiles for drug concentration, ΔQTcF and ΔHR to evaluate presence of any time delay between concentration and QTc interval and to evaluate any heart rate effects. There does not seem to be any delayed effect on QTcF changes or any heart rate effects. Further, visual comparison of the placebo data with the various drug treatment arms do not reveal any direct dose-response relationship.

Figure 4: Drug concentration, Δ QTcF, and heart rate plotted on the same time axis. Error bars illustrate mean \pm SD for concentration and 90% CI for Δ HR and Δ QTcF



Linearity of the C-QTc relationship can be assessed graphically by plotting drug concentrations versus observed $\Delta\Delta$ QTcF (calculated by subtracting the placebo group's mean Δ QTcF from Δ QTcF of the active treatment groups for each time point) over a linear regression line and a non-parametric smoother. Ideally the non-parametric smoother should track the linear regression line over the span of the observed concentrations. The interpretation can be further facilitated by dividing concentrations in bins with equal number of observations and plotting the median or midpoint of the concentrations in each of the bins against the corresponding $\Delta\Delta$ QTcF mean and \pm SD. The relationship between $\Delta\Delta$ QTcF and edaravone concentrations is visualized in Figure 5.

Figure 5: $\Delta\Delta$ QTcF vs. Edaravone Concentration; The points and bars represent $\Delta\Delta$ QTcF mean \pm SD at the median concentration in a bin. Dashed black line represents linear regression; Red line represents a non-parametric smoother.



Further, the data was modeled with a prespecified linear mixed effect model as defined below:

$$\Delta QTc_{ijk} = (\mu + TRT_j + t_k + \eta_{\mu,i}) + \theta_0(B_{QTc,i} - \bar{B}) + (\theta_1 + \eta_{C,i})C_{ijk} + \varepsilon_{ijk}$$

Where i is the i^{th} subject, j is the j^{th} treatment, k is the k^{th} time point relative to dosing, μ is the intercept, TRT_j is the j^{th} treatment effect, t_k is the k^{th} time effect, $B_{QTc,i}$ is the baseline QTc for the i^{th} subject (for parallel design), \bar{B} is the population mean baseline QTc, C_{ijk} is the concentration at the k^{th} time point for Treatment j for Subject i . $\eta_{\mu,i}$ and $\eta_{C,i}$ are the subject-specific random effects for the intercept and slope, respectively, having mean $[0,0]$. ε are independent residuals having mean zero and variance σ^2 .

The final fixed and random effect parameters for the model are listed in Table 14 and Table 15.

Table 14: Edaravone concentration-QTcF relationship fixed effects parameter estimates and their associated precision, based on Kenward-Roger approximation

Fixed effect parameter	Estimate	Lower 95% CI	Upper 95% CI	Relative standard error (%)	p
(Intercept)	0.9616691	-3.2344514	5.15778960	219.56182	0.651
TIME0.5	-4.5918961	-8.0405581	-1.14323407	-38.21463	0.00938
TIME1	-1.4834740	-5.0111822	2.04423427	-120.99996	0.411
TIME2	-0.8573579	-4.4403085	2.72559277	-212.64401	0.64
TIME4	-8.4641320	-11.9529205	-4.97534360	-20.97330	<0.001
TIME8	-8.2391169	-11.8260257	-4.65220813	-22.15208	<0.001
TIME12	-4.8865703	-8.5328132	-1.24032732	-37.96752	0.00906
TIME16	1.6207617	-3.1358168	6.37734022	149.32165	0.504
TIME20	2.7457617	-2.0108168	7.50234022	88.14123	0.258
TIME24	-3.0891978	-6.9725706	0.79417489	-63.95587	0.121
TIME30	-12.6917383	-17.4483168	-7.93515978	-19.06869	<0.001
TIME36	-3.0042383	-7.7608168	1.75234022	-80.55779	0.216
TIME42	-2.0667383	-6.8233168	2.68984022	-117.09988	0.394
TIME48	-4.6138997	-7.8284033	-1.39939604	-35.44411	0.00501
ACTIVE1	-1.4745593	-6.1067891	3.15767051	-156.69367	0.528
I(QTCF.BS - QTCF.mB)	-0.2365981	-0.3830676	-0.09012852	-30.70576	0.00233
CONC	2.0209257	-5.6685134	9.71036473	184.61039	0.602

Table 15: Edaravone concentration-QTcF relationship random effects parameter estimates and their associated precision, based on log-likelihood profiling

Random effect parameter	Estimate (sd)	Lower 95% CI	Upper 95% CI
SUBJID (Intercept)	6.254566	4.694272	7.850154

Random effect parameter	Estimate (sd)	Lower 95% CI	Upper 95% CI
SUBJID.1 CONC	9.553132	3.335016	16.960495
Residual error	7.842786	7.236301	8.266950

Based on the output, edaravone concentration- Δ QTcF relationship was not statistically significantly, with the slope estimated being 2.02 (95% CI: [-5.67; 9.71]) ms/(μ g/ml) (p-value=0.602).

To rule out a clinically significant effect on QTc, we need to estimate the $\Delta\Delta$ QTcF at C_{max} for the highest tested dose. The upper 90% CI of $\Delta\Delta$ QTcF at C_{max} should not include 10 ms. $\Delta\Delta$ QTcF is defined as the model-derived difference between Δ QTcF at concentration of interest and model-derived Δ QTcF for placebo at concentration 0, (ACTIVE=0). In this case the concentration of interest is C_{max} .

$$\Delta\Delta QTcF = \Delta QTcF_{C=C_{max},ACTIVE=1} - \Delta QTcF_{C=0,ACTIVE=0}$$

Table 16 below shows Δ QTcF and $\Delta\Delta$ QTcF estimates at the mean C_{max} of 1.16 μ g/ml for the highest dose level (0.2 mg/kg bolus + 0.5 mg/kg/h IV infusion for 24 hours). The predicted upper bound of 90% CI for the response at the mean C_{max} with highest dose (1.16 μ g/mL) was below regulatory threshold of 10 ms (4.86 ms and 7.98 ms respectively for Δ QTcF and $\Delta\Delta$ QTcF).

Table 16: Edaravone Δ QTcF and $\Delta\Delta$ QTcF estimates at the mean C_{max} for the highest dose level (0.2 mg/kg bolus + 0.5 mg/kg/h IV infusion for 24 hours)

Exposure	Parameter	Concentration (μ g/ml)	Estimate	Lower 90% CI	Upper 90% CI
Mean Cmax	Δ QTcF	1.16	-1.76	-8.39	4.86
	$\Delta\Delta$ QTcF	1.16	0.87	-6.24	7.98

Model performance was assessed by plotting observed and model estimated Δ QTcF versus the observed edaravone concentrations in Figure 6.

Figure 6: Goodness of fit showing observed and estimated Δ QTcF vs. drug concentrations. The points and bars represent Δ QTcF mean and 90% CI at the median concentration in a bin. Black line represents predictions from the prespecified Concentration- Δ QTcF model. The shaded area represents the 90% CI of the prediction.

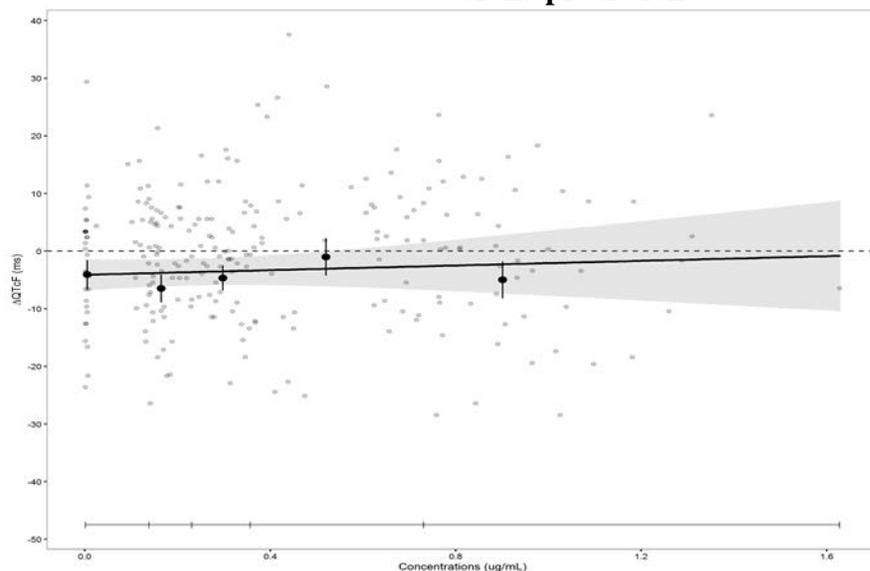
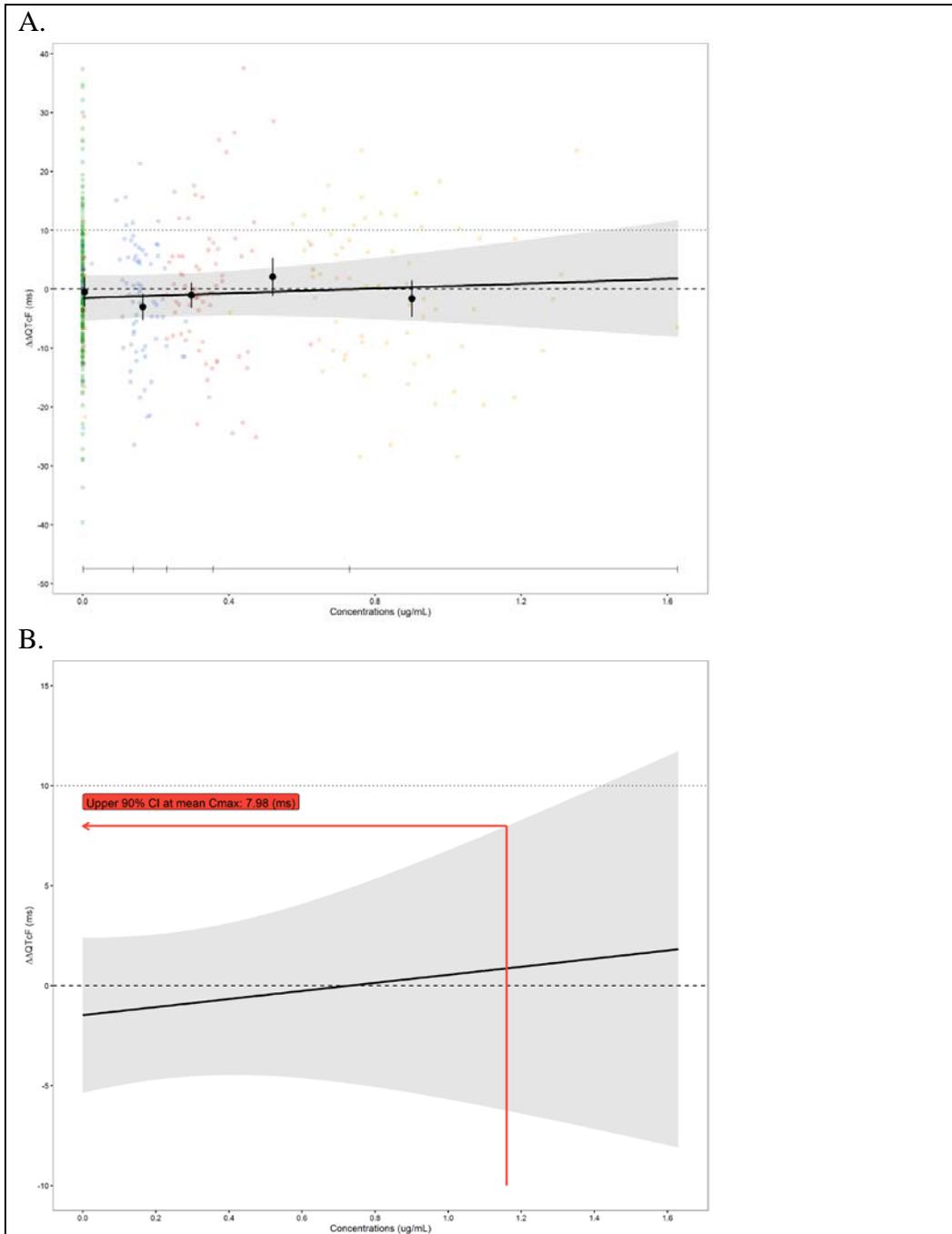


Figure 7 illustrates the relationship between $\Delta\Delta$ QTcF and plasma concentrations of edaravone. The observed data in panel A is calculated arithmetically (same as that shown in Figure 5). Both panel A and B have model derived $\Delta\Delta$ QTcF as shown in equation above. Panel B illustrates the concentration- $\Delta\Delta$ QTcF relationship without the observed data. This plot can help in interpreting the effects on $\Delta\Delta$ QTcF following different doses with different C_{\max} . The figure also shows the predicted upper bound of 90% CI for $\Delta\Delta$ QTcF at the mean C_{\max} (1.16 $\mu\text{g/mL}$) for the highest dose in the study.

Figure 7: Prediction plots showing observed and estimated $\Delta\Delta\text{QTcF}$ versus drug concentrations. Panel A shows observed $\Delta\Delta\text{QTcF}$ as scatter points and bins. The points and bars represent $\Delta\Delta\text{QTcF}$ mean and 90% CI at the median concentration in a bin. The black line represents predictions from the concentration-QTcF model prespecified by the reviewer. The shaded area represent the 90% CI of the prediction. Panel B shows model estimated $\Delta\Delta\text{QTcF}$ alone. Arrow indicates the $\Delta\Delta\text{QTcF}$ upper 90% CI at mean C_{max} for the highest dose in the study.



5.4 CLINICAL ASSESSMENTS

5.4.1 Safety assessments

None of the events identified to be of clinical importance per the ICH E 14 guidelines (i.e. syncope, seizure, significant ventricular arrhythmias or sudden cardiac death) occurred in this study.

5.4.2 ECG assessments

Paper ECG tracings were not submitted. ECG acquisition and interpretation in this study can't be determined.

6 APPENDIX

6.1 HIGHLIGHTS OF CLINICAL PHARMACOLOGY

Therapeutic dose and exposure	<p>Clinical dosing regimen: 60 mg/man/h, infusion, once a daily for 14 days Mean (%CV) Cmax and AUC of Simulated data from PPK model</p> <p>Single dose Cmax: 1046.6 ng/mL (11.2), AUC: 1362.3 ng·h/mL (14.3)</p> <p>At the steady state Cmax: 1048.6 ng/mL (11.2), AUC: 1374.3 ng·h/mL (14.5) Table 2.7.2.3.3-1</p>	
Maximum tolerated dose	Maximum doses tested shown below were well tolerated.	
Principal adverse events	<p>There were no common drug-related AEs across the 5 Clinical Pharmacology studies MCI186-01, MCI186-10, MCI186-14, MCI186-E01 and MCI186-E02. Drug-related AEs ≥30% reported in E02 study included Infusion site pain [0.2 mg/kg bolus + 0.5mg/kg/h infusion, 6 (60.0%)] and Diarrhoea [0.2 mg/kg bolus + 0.5mg/kg/h infusion, 3 (30.0%)]. MCI186-N03</p>	
Maximum dose tested	Single Dose	1.5 mg/kg/40 min (MCI186-01) M2.7.2.2.2.1
	Multiple Dose	1 mg/kg/40 min/day for 7 days (MCI186-01) M2.7.2.2.2.1
Exposures Achieved at Maximum Tested Dose	Single Dose	<p>Mean (%CV) Cmax: 3060.73 ng/mL (7.7) AUC: 3005 ng·h/mL (7.9) MCI186-01 CSR</p>
	Multiple Dose	<p>Range of Cmax: 1616.21-1819.13 ng/mL Mean (%CV) AUC: 1669 ng·h/mL (5.3) MCI186-01 CSR</p>
Range of linear PK	<p>Observed data Cmax and AUC increased depending on dose over 0.2–1.5 mg/kg for 40 min infusion (MCI186-01, 4 doses) and 0.05–0.2 mg/kg bolus + 0.125–0.5 mg/kg/h for 23.95 h infusion (MCI186-E02, 3 doses). M2.7.2.2.2.1 and M2.7.2.2.2.5</p> <p>Simulation data Simulated data of virtual ALS patient in US from PPK model, AUC was 602.6, 1374.3, and 3161.1 ng·h/mL for the 30 , 60 , and 120 mg/man/h infused repeated dosing regimens for 14 days, respectively. PPK report 002525</p>	
Accumulation at steady state	<p>Observed data 1 mg/kg/40 min/day for 7 days M2.7.2.2.2.1 Mean (%CV) AUC 1st day: 1474 ng·h/mL (8.0) 7th day: 1669 ng·h/mL (5.3)</p> <p>Simulated data of virtual ALS patient in US from PPK model 60 mg/man/60 min/day for 14 days Table 2.7.2.3.3-1 Mean (%CV) AUC 1st day: 1362.3 ng·h/mL (14.3) 14th day: 1374.3 ng·h/mL (14.5)</p>	
Metabolites	<p>Sulfate, glucuronide M2.7.2.2.2 Neither the sulfate nor the glucuronide have radical scavenging activities. M2.6.2.2.6</p>	

Absorption	Absolute/Relative Bioavailability	Not done
	Tmax	Tmax were approximately at the end of infusion in each clinical study. M2.7.2.2.2
Distribution	Vd/F or Vd (L/kg)	Distribution volume at steady state Mean (CV%) 0.93 L/kg (21.5), Adult, MCI186-10 0.86 L/kg (11.6), Elderly, MCI186-10 Table 2.7.2.2.2-5 0.73 L/kg (42.3), MCI186-14 Table 2.7.2.2.2-8
	% bound	Serum protein binding ratio in human: 91.0–91.9 % M2.6.4.4.2-1
Elimination	Route	Primary route; urine M2.7.2.2.2 Mean total urinary excretion of edaravone, sulfate and glucuronide (% of dose) 82.12–90.43 (MCI186-01) Table 2.7.2.2.2-2 92.493–97.020 (MCI186-E02) Table 2.7.2.2.2-14
	Terminal t _{1/2} (hr)	Range of mean t _{1/2} Edaravone 4.38–6.01 (MCI186-01) Table 2.7.2.2.2-1 and -3 3.42 (MCI186-14) Table 2.7.2.2.2-8 1.48–3.53 (MCI186-E01) Table 2.7.2.2.2-11 5.419–6.965 (MCI186-E02) Table 2.7.2.2.2-12 Sulfate 2.028–2.781 (MCI186-E02) MCI186-E02 CSR Glucuronide 2.185–2.837 (MCI186-E02) MCI186-E02 CSR
	CL/F or CL (mL/kg/hr)	Range of mean CL 683.5 (Adult, MCI186-10) MCI186-10 CSR 695.1 (Elderly, MCI186-10) MCI186-10 CSR 835 (MCI186-14) Table 2.7.2.2.2-8 738–1296 (MCI186-E01) Table 2.7.2.2.2-11 531.1–679.9 (MCI186-E02) Table 2.7.2.2.2-12

Intrinsic Factors	Age	There were no age effects observed on pharmacokinetics of MCI-186 in MCI186-10 study. Table 2.7.2.2.2-5 C _{max} (ng/mL): 887.6 (adult), 1040.7 (elderly) AUC (ng·h/mL): 742 (adult), 725 (elderly) Age is not an influence factor for PK parameters based on PPK analysis. M2.7.2.3.3
	Sex	There were no gender effects observed on pharmacokinetics of MCI-186 in MCI186-E02 study. Table 2.7.2.2.2-13 AUC (ng·h/mL) 0.125 mg/kg/h+3-min bolus 0.05 mg/kg/h: 4449.2 (male), 5038.8 (female) 0.25 mg/kg/h+3-min bolus 0.1 mg/kg/h: 10999.6 (male), 8892.2 (female) 0.5 mg/kg/h+3-min bolus 0.2 mg/kg/h: 24992.2 (male), 23278.7 (female) Sex is not an influence factor for PK parameters based on PPK analysis. M2.7.2.3.3
	Race	Race was statistically significant predictors of peripheral volume of distribution (V ₂) from PPK analysis. The V ₂ of distribution is 26% higher for Caucasian subjects than for Japanese subjects. No significant differences were observed for C _{max} or AUC between both race from simulation of PPK model. M2.7.2.3.3
	Hepatic & Renal Impairment	No data. Human PK studies in patients with renal or hepatic impairment will be conducted in parallel with the NDA review. M2.7.2.4
Extrinsic Factors	Drug interactions	Human DDI study was not conducted. But in vitro studies indicated that edaravone PK is not affected by concomitant drugs. M2.7.2.3.1.2
	Food Effects	No data
Expected High Clinical Exposure Scenario	Not detected. Human PK studies in patients with renal or hepatic impairment will be conducted in parallel with the NDA review. M2.7.2.4	
Preclinical Cardiac Safety	Edaravone did not inhibit hERG current at 10 ⁻⁴ mol/L. In the anesthetized dog, intravenous dose of edaravone did not affect ECG up to the highest dose of 100 mg/kg. M2.6.2.4.2	
Clinical Cardiac Safety	The third party cardiologist reviewed all nonclinical data, the available ECG data and AE profiles from clinical studies and postmarketing reports, suggesting no important clinical concern of cardiac issues caused by edaravone. The summary of the cardiac review with ECG assessment is submitted to the Agency under this NDA. M2.7.2.2.3.3	

6.2 SCHEDULE OF ASSESSMENTS

Study Day	Screening	Assessment Period				Follow-up		
	-28 to -2	-1 (-16h)	Day 1	Day 2	Day 3	1 week (7d ± 2d)	4 weeks (28d ± 4d)	12 weeks (84d ± 8d)
Confinement		X	X	X	X			
Outpatient	X					X	X	X
Informed Consent and Medical History ¹	X							
Demographics	X							
Physical Examination ²	X	X	X		X	X		
Neurological assessment ³	X					X	X	X
Height	X							
Body weight ⁴	X	X						
Vital signs ⁵	X	X	X	X	X	X		
Inclusion/Exclusion Criteria	X							
12-lead ECG ⁶	X	X	X	X	X	X		
Clinical Laboratory ⁷	X	X		X		X		
Urine Drug screen	X	X						
Alcohol breath test	X	X				X	X	X
Alcohol blood group 2 and 3				X				
HAV (IgM), HBsAg, HCV and HIV 1/2 tests	X							
Randomisation (pre-dose)			X					
Study Drug Administration ⁸			X					
Previous and Concomitant Medication	X	X	X	X	X	X	X	X
PK Blood Sampling, see Table 6			X	X	X			
PK Urine Sampling ⁹		X	X	X	X			
Adverse Events ¹⁰		X	X	X	X	X	X	X

1 Including post-menopausal test for female subjects, spontaneous amenorrhea between six (6) and twelve (12) months.

2 Physical examination at Day -1, Day 1 at 6h after start of infusion and at Day 3 before discharge.

3 Neurological assessment: examination was performed at screening by two independent investigators and at the one (1), four (4) and twelve (12) week follow-up visits by one investigator. QST at screening was performed by two independent investigators, and at the four (4) and twelve (12) week follow-up visits by one investigator. The questionnaire was performed at screening and at the one (1), four (4) and twelve (12) week follow-up visits by one investigator. The QST measurement was repeated by a second investigator in case the values differed from baseline more than 25% or more than 2x the SD as indicated by the device manual. Tuning Fork Test at screening and at the four (4)

and twelve (12) week follow-up visits (for Group 3 only).

4 Body weight at Day -1 for dose calculation.

5 Vital signs: Blood pressure, pulse rate, oral body temperature: at screening; Day -1, Day 1: pre-dose, 30min, 1h, 2h, 4h, 8h, 12h, 16h, 20h, 24h, 30h, 36h, 42h, 48h after start of the infusion and at the one (1) week follow-up visit.

6 ECG: same time points as those for vital signs

7 Laboratory assessments: haematology, clinical chemistry and urinalysis: at screening; Day -1, Day 2: at 31h post-dose and at the one (1) week follow-up visit.

8 Intravenous bolus given over 3 min followed by an infusion over 23h57min.

9 PK-Urine sampling: Day -1: -12h - 0h (pre-dose); Day 1: 0h - 24h (end of infusion), 24h - 48h (after the start of infusion). Note that urine will be collected every micturition, and edaravone and its sulphate and glucuronide metabolite concentrations will be determined.

10 Adverse events were actively asked for at the same time points as those for vital signs and ECG and continual assessment till week twelve (12).

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

/s/

DHANANJAY D MARATHE
12/19/2016

MOH JEE NG
12/19/2016

QIANYU DANG
12/19/2016

MICHAEL Y LI
12/19/2016

CHRISTINE E GARNETT
12/19/2016

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]

Application Information		
NDA # 209176 BLA#	NDA Supplement #: S- BLA Supplement #: S-	Efficacy Supplement Category: <input type="checkbox"/> New Indication (SE1) <input type="checkbox"/> New Dosing Regimen (SE2) <input type="checkbox"/> New Route Of Administration (SE3) <input type="checkbox"/> Comparative Efficacy Claim (SE4) <input type="checkbox"/> New Patient Population (SE5) <input type="checkbox"/> Rx To OTC Switch (SE6) <input type="checkbox"/> Accelerated Approval Confirmatory Study (SE7) <input type="checkbox"/> Labeling Change With Clinical Data (SE8) <input type="checkbox"/> Manufacturing Change With Clinical Data (SE9) <input type="checkbox"/> Animal Rule Confirmatory Study (SE10)
Proprietary Name: Radicava Established/Proper Name: edaravone Dosage Form: IV injection Strengths: 30mg / 100ml		
Applicant: Mitsubishi Tanabe Pharma Corporation Agent for Applicant (if applicable): Douglas N. Dobak		
Date of Application: 06/16/2016 Date of Receipt: 06/16/2016 Date clock started after UN:		
PDUFA/BsUFA Goal Date: 02/16/17		Action Goal Date (if different):
Filing Date: 08/15/16		Date of Filing Meeting: 07/13/16
Chemical Classification (original NDAs only) : <input checked="" type="checkbox"/> Type 1- New Molecular Entity (NME); NME <input type="checkbox"/> Type 2- New Active Ingredient; New Active Ingredient and New Dosage Form; New Active Ingredient and New Combination <input type="checkbox"/> Type 3- New Dosage Form; New Dosage Form and New Combination <input type="checkbox"/> Type 4- New Combination <input type="checkbox"/> Type 5- New Formulation or New Manufacturer <input type="checkbox"/> Type 7- Drug Already Marketed without Approved NDA <input type="checkbox"/> Type 8- Partial Rx to OTC Switch		
Proposed indication(s)/Proposed change(s): treatment of amyotrophic lateral sclerosis (ALS)		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:		<input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) <hr/> <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" review found at:</i> http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499		

Type of BLA	<input type="checkbox"/> 351(a) <input type="checkbox"/> 351(k)
<i>If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team</i>	
Review Classification:	<input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority
<i>The application will be a priority review if:</i>	<input type="checkbox"/> Pediatric WR
<ul style="list-style-type: none"><i>A complete response to a pediatric Written Request (WR) was included (a partial response to a WR that is sufficient to change the labeling should also be a priority review – check with DPMH)</i><i>The product is a Qualified Infectious Disease Product (QIDP)</i><i>A Tropical Disease Priority Review Voucher was submitted</i><i>A Pediatric Rare Disease Priority Review Voucher was submitted</i>	<input type="checkbox"/> QIDP <input type="checkbox"/> Tropical Disease Priority Review Voucher <input type="checkbox"/> Pediatric Rare Disease Priority Review Voucher
Resubmission after withdrawal? <input type="checkbox"/>	Resubmission after refuse to file? <input type="checkbox"/>
Part 3 Combination Product? <input type="checkbox"/>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Pre-filled biologic delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)
<i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>	

<input type="checkbox"/> Fast Track Designation <input type="checkbox"/> Breakthrough Therapy Designation <i>(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)</i> <input type="checkbox"/> Rolling Review <input checked="" type="checkbox"/> Orphan Designation	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies (FDCA Section 505B) <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
<input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC	
Other:	

Collaborative Review Division (if OTC product): N/A

List referenced IND Number(s): 126396

Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA/BsUFA and Action Goal dates correct in tracking system? <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Are the established/proper and applicant names correct in tracking system? <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

<i>to the supporting IND(s) if not already entered into tracking system.</i>				
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, orphan drug)? <i>Check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:</i> http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm <i>If no, ask the document room staff to make the appropriate entries.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at:</i> http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
If yes, explain in comment column.				
If affected by AIP, has OC been notified of the submission? If yes, date notified:	<input type="checkbox"/>	<input type="checkbox"/>		
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet)/Form 3792 (Biosimilar User Fee Cover Sheet) included with authorized signature?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<u>User Fee Status</u> <i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i>	Payment for this application (<i>check daily email from UserFeeAR@fda.hhs.gov</i>): <input type="checkbox"/> Paid <input checked="" type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required			
<i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i>	Payment of other user fees: <input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears			
<u>User Fee Bundling Policy</u> <i>Refer to the guidance for industry, Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees at:</i> http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf	Has the user fee bundling policy been appropriately applied? <i>If no, or you are not sure, consult the User Fee Staff.</i> <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No			
505(b)(2) (NDAs/NDA Efficacy Supplements only)	YES	NO	NA	Comment
Is the application a 505(b)(2) NDA? (<i>Check the 356h form,</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		

cover letter, and annotated labeling). If yes , answer the bulleted questions below:					
• Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?		<input type="checkbox"/>	<input type="checkbox"/>		
• Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].		<input type="checkbox"/>	<input type="checkbox"/>		
• Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?		<input type="checkbox"/>	<input type="checkbox"/>		
<i>If you answered yes to any of the above bulleted questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs for advice.</i>					
• Is there unexpired exclusivity on another listed drug product containing the same active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)?		<input type="checkbox"/>	<input type="checkbox"/>		
Check the Electronic Orange Book at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm					
If yes , please list below:					
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration		
<i>If there is unexpired, 5-year exclusivity remaining on another listed drug product containing the same active moiety, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.</i>					
Exclusivity	YES	NO	NA	Comment	
Does another product (same active moiety) have orphan exclusivity for the same indication? Check the Orphan Drug Designations and Approvals list at: http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm	<input type="checkbox"/>	<input checked="" type="checkbox"/>			
If another product has orphan exclusivity , is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
<i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i>					
NDAs/NDA efficacy supplements only: Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Sponsor requests orphan exclusivity	
If yes , # years requested: 7					
Note: An applicant can receive exclusivity without requesting it;					

<i>therefore, requesting exclusivity is not required.</i>				
NDAs only: Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? <i>If yes, contact the Orange Book Staff (CDER-Orange Book Staff).</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
BLAs only: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act? <i>If yes, notify Marlene Schultz-DePalo, CDER Purple Book Manager</i> <i>Note: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

Format and Content				
<i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic) <input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	YES	NO	NA	Comment
If electronic submission, does it follow the eCTD guidance? ¹ If not, explain (e.g., waiver granted).	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Index: Does the submission contain an accurate comprehensive index?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Is the submission complete as required under 21 CFR 314.50 (NDAs/NDA efficacy supplements) or under 21 CFR 601.2 (BLAs/BLA efficacy supplements) including:	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

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<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

<input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only)				
If no, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
If yes, BLA #				
Forms and Certifications				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397/3792), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i>				
<i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i>				

<i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>				
Debarment Certification	YES	NO	NA	Comment
Is a correctly worded Debarment Certification included with authorized signature? <i>Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i> <i>Note: Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as, “To the best of my knowledge...”</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? <i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i> <i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? <i>If yes, date consult sent to the Controlled Substance Staff: 6/27/16</i> <u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Pediatrics	YES	NO	NA	Comment
<u>PREA</u> Does the application trigger PREA? <i>If yes, notify PeRC@fda.hhs.gov to schedule required PeRC meeting²</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		

<i>Note: NDAs/BLAs/efficacy supplements for new active ingredients (including new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i>				
If the application triggers PREA , is there an agreed Initial Pediatric Study Plan (iPSP)? <i>If no, may be an RTF issue - contact DPMH for advice.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
If required by the agreed iPSP , are the pediatric studies outlined in the agreed iPSP completed and included in the application? <i>If no, may be an RTF issue - contact DPMH for advice.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<u>BPCA:</u> Is this submission a complete response to a pediatric Written Request? <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i>	<input type="checkbox"/>	<input type="checkbox"/>		
Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted? <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
REMS	YES	NO	NA	Comment
Is a REMS submitted? <i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
Prescription Labeling	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input checked="" type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL	<input type="checkbox"/>	<input type="checkbox"/>		

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<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/ucm027829.htm>

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<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/ucm027837.htm>

format?				
<i>If no, request applicant to submit SPL before the filing date.</i>				
Is the PI submitted in PLR format? ⁴	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>				
For applications submitted on or after June 30, 2015: Is the PI submitted in PLLR format? ⁵	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Has a review of the available pregnancy and lactation data been included?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
For applications submitted on or after June 30, 2015: If PI not submitted in PLLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<i>If no waiver or deferral, request applicant to submit labeling in PLR/PLLR format before the filing date.</i>				
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office in OPQ (OBP or ONDP)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
OTC Labeling	<input checked="" type="checkbox"/> Not Applicable			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment

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<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

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<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

Is electronic content of labeling (COL) submitted? <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>		
Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
If representative labeling is submitted, are all represented SKUs defined? <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
All labeling/packaging sent to OSE/DMEPA?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) <i>If yes, specify consult(s) and date(s) sent:</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	QT
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? Date(s):	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
<i>If yes, distribute minutes before filing meeting</i>				
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): 12/9/15	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If yes, distribute minutes before filing meeting</i>				
Any Special Protocol Assessments (SPAs)? Date(s):	<input type="checkbox"/>			
<i>If yes, distribute letter and/or relevant minutes before filing meeting</i>				

ATTACHMENT

MEMO OF FILING MEETING

DATE: 7/13/16

BACKGROUND: Mitsubishi Tanabe Pharma's compound MCI-186 (edaravone), a molecule with free radical scavenging effects, was approved in Japan for treatment of acute ischemic stroke in 2001. On June 26, 2015, edaravone was approved in Japan for the treatment of ALS.

A teleconference between sponsor representatives and DNP was held on December 22, 2014, to discuss the high-level efficacy and safety data and the path to approval in the United States.

On May 12, 2015, edaravone received orphan designation in the US for the treatment of ALS.

On June 16, 2015, a pre-IND meeting was held to discuss the efficacy findings of the phase 3 study of edaravone for the treatment of ALS and to obtain agreement as to the regulatory pathway needed for approval.

On October 22, 2015, a Chemistry, Manufacturing, and Controls-only pre-NDA meeting was held.

On December 9, 2015, a pre-NDA meeting was held to discuss the content and format of the NDA.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Susan Daugherty, Jack Dan	YES
	CPMS/TL:	Jackie Ware	YES
Cross-Discipline Team Leader (CDTL)	Nicholas Kozauer		YES
Division Director/Deputy	Billy Dunn		YES
Office Director/Deputy	Ellis Unger Bob Temple		YES YES
Clinical	Reviewer:	Chris Breder	YES
	TL:	Nicholas Kozauer	YES

Social Scientist Review (<i>for OTC products</i>)	Reviewer:		
	TL:		
OTC Labeling Review (<i>for OTC products</i>)	Reviewer:		
	TL:		
Clinical Microbiology (<i>for antimicrobial products</i>)	Reviewer:		
	TL:		
Clinical Pharmacology	Reviewer:	Xinning Yang	YES
	TL:	Sreedharan Sabarinath	YES
• Genomics	Reviewer:		
• Pharmacometrics	Reviewer:		
Biostatistics	Reviewer:	Tristan Massie	NO
	TL:	Kun Jin	YES
Nonclinical (Pharmacology/Toxicology)	Reviewer:	David Carbone	YES
	TL:	Lois Freed	YES
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Product Quality (CMC) Review Team:	ATL: CMC lead	Wendy Wilson Martha Heimann	YES YES
	RBPM:	Dahlia Woody	
• Drug Substance	Reviewer:	Sithamalli Chandramouli/Kasturi Srivasaachar	
• Drug Product	Reviewer:	Dan Berger/Wendy Wilson	
• Process	Reviewer:	Kumar Janoria/Edwin Joa	
• Microbiology	Reviewer:	Eric Adeeku/Maotong Zhou	
• Facility	Reviewer:	Aditi Thakur/Christina Capacci-Daniel	
• Biopharmaceutics	Reviewer:	Banu Zolnik/Okpo Eradiri	
• Immunogenicity	Reviewer:	N/A	
• Labeling (BLAs only)	Reviewer:	N/A	
• Other (e.g., Branch Chiefs, EA Reviewer)			
OMP/OMPI/DMPP (Patient labeling:	Reviewer:		

MG, PPI, IFU)			
	TL:		
OMP/OPDP (PI, PPI, MedGuide, IFU, carton and immediate container labels)	Reviewer:		
	TL:		
OSE/DMEPA (proprietary name, carton/container labels)	Reviewer:	Lolita White Ebony Whaley	YES YES
	TL:		
OSE/DRISK (REMS)	Reviewer:		
	TL:		
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		
Bioresearch Monitoring (OSI)	Reviewer:	Cara Alfaro	YES
	TL:		
Controlled Substance Staff (CSS)	Reviewer:	Bonson	
	TL:		
Other reviewers/disciplines			
<ul style="list-style-type: none"> • Discipline <p>*For additional lines, highlight this group of cells, copy, then paste: select "insert as new rows"</p>	Reviewer:		
	TL:		
Other attendees			
*For additional lines, right click here and select "insert rows below"			

FILING MEETING DISCUSSION:

<p>GENERAL</p> <ul style="list-style-type: none"> • 505 b)(2) filing issues: <ul style="list-style-type: none"> ○ Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? ○ Did the applicant provide a scientific "bridge" demonstrating the relationship 	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------	----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------

<p>between the proposed product and the referenced product(s)/published literature?</p> <p>Describe the scientific bridge (e.g., information to demonstrate sufficient similarity between the proposed product and the listed drug(s) such as BA/BE studies or to justify reliance on information described in published literature):</p>	
<ul style="list-style-type: none"> Per reviewers, are all parts in English or English translation? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Electronic Submission comments <p>List comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> No comments
<p>CLINICAL</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical study site(s) inspections(s) needed? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Advisory Committee Meeting needed? <p>Comments:</p> <p><i>If no, for an NME NDA or original BLA, include the reason. For example:</i></p> <ul style="list-style-type: none"> <i>this drug/biologic is not the first in its class</i> <i>the clinical study design was acceptable</i> <i>the application did not raise significant safety or efficacy issues</i> <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i> 	<input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined Reason:
<ul style="list-style-type: none"> If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? 	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO

Comments:	
CONTROLLED SUBSTANCE STAFF <ul style="list-style-type: none"> Abuse Liability/Potential Comments: DARRTS 07/05/16	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
CLINICAL MICROBIOLOGY Comments:	<input type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
CLINICAL PHARMACOLOGY Comments:	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical pharmacology study site(s) inspections(s) needed? 	<input type="checkbox"/> YES <input type="checkbox"/> NO
BIOSTATISTICS Comments: DARRTS 07/11/16	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) Comments: DARRTS 07/15/16	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
PRODUCT QUALITY (CMC) Comments:	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<u>New Molecular Entity (NDAs only)</u> <ul style="list-style-type: none"> Is the product an NME? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<u>Environmental Assessment</u> <ul style="list-style-type: none"> Categorical exclusion for environmental assessment 	<input checked="" type="checkbox"/> YES

(EA) requested? If no , was a complete EA submitted? Comments:	<input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<u>Facility Inspection</u> <ul style="list-style-type: none"> Establishment(s) ready for inspection? Comments:	<input type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<u>Facility/Microbiology Review (BLAs only)</u> Comments:	<input type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<u>CMC Labeling Review (BLAs only)</u> Comments:	<input type="checkbox"/> Review issues for 74-day letter
APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs) <ul style="list-style-type: none"> Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? If so, were the late submission components all submitted within 30 days? 	<input type="checkbox"/> N/A <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> What late submission components, if any, arrived after 30 days? 	

<ul style="list-style-type: none"> Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Is a comprehensive and readily located list of all clinical sites included or referenced in the application? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

REGULATORY PROJECT MANAGEMENT

Signatory Authority: Ellis Unger

Date of Mid-Cycle Meeting (for NME NDAs/BLAs in “the Program” PDUFA V): 11/16/16??

21st Century Review Milestones (see attached) (listing review milestones in this document is optional):

Comments:

REGULATORY CONCLUSIONS/DEFICIENCIES

<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	<p>The application, on its face, appears to be suitable for filing.</p> <p><u>Review Issues:</u></p> <p><input checked="" type="checkbox"/> No review issues have been identified for the 74-day letter. <input type="checkbox"/> Review issues have been identified for the 74-day letter.</p> <p><u>Review Classification:</u></p> <p><input checked="" type="checkbox"/> Standard Review <input type="checkbox"/> Priority Review</p>

ACTION ITEMS

<input checked="" type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into the electronic archive (e.g., chemical classification, combination product classification, orphan drug).
<input type="checkbox"/>	If RTF, notify everyone who already received a consult request, OSE PM, and RBPM

<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	If priority review, notify applicant in writing by day 60 (see CST for choices)
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input checked="" type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input type="checkbox"/>	Update the PDUFA V DARRTS page (for applications in the Program)
<input type="checkbox"/>	Other

Annual review of template by OND ADRA's completed: September 2014

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

/s/

JACK DAN
07/26/2016