

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**209176Orig1s000**

**ADMINISTRATIVE and CORRESPONDENCE  
DOCUMENTS**

# ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION <sup>1</sup>		
NDA # 209176 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: <i>(an action package is not required for SE8 or SE9 supplements)</i>
Proprietary Name: Radicava Established/Proper Name: edaravone Dosage Form: Injection		Applicant: Mitsubishi Tanabe Pharma Corporation Agent for Applicant (if applicable): Douglas N. Dobak
RPM: Jack Dan/Susan Daugherty		Division: Neurology
NDA Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)  BLA Application Type: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a) Efficacy Supplement: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a)		<b><u>For ALL 505(b)(2) applications, two months prior to EVERY action:</u></b> <ul style="list-style-type: none"> <li><b>Review the information in the 505(b)(2) Assessment and submit the draft<sup>2</sup> to CDER OND IO for clearance.</b></li> <li><b>Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)</b> <ul style="list-style-type: none"> <li><input type="checkbox"/> No changes</li> <li><input type="checkbox"/> New patent/exclusivity <i>(notify CDER OND IO)</i></li> </ul> </li> </ul> Date of check: _____  <i>Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</i>
❖ Actions		
<ul style="list-style-type: none"> <li>Proposed action</li> <li>User Fee Goal Date is 06/16/17</li> </ul>		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> <li>Previous actions <i>(specify type and date for each action taken)</i></li> </ul>		<input checked="" type="checkbox"/> None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see <a href="http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf">http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf</a> ). If not submitted, explain _____		<input type="checkbox"/> Received
❖ Application Characteristics <sup>3</sup>		

<sup>1</sup> The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.

<sup>2</sup> For resubmissions, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

<sup>3</sup> Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA.

Review priority:  Standard  Priority  
 Chemical classification (new NDAs only): Type 1, NME  
 (confirm chemical classification at time of approval)

- |   |   |
|---|---|
| <input type="checkbox"/> Fast Track                         | <input type="checkbox"/> Rx-to-OTC full switch    |
| <input type="checkbox"/> Rolling Review                     | <input type="checkbox"/> Rx-to-OTC partial switch |
| <input checked="" type="checkbox"/> Orphan drug designation | <input type="checkbox"/> Direct-to-OTC            |
| <input type="checkbox"/> Breakthrough Therapy designation   |   |

(NOTE: Set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager;  
 Refer to the "RPM BT Checklist for Considerations after Designation Granted" for other required actions: [CST SharePoint](#))

NDAs: Subpart H

- Accelerated approval (21 CFR 314.510)  
 Restricted distribution (21 CFR 314.520)

Subpart I

- Approval based on animal studies

- Submitted in response to a PMR  
 Submitted in response to a PMC  
 Submitted in response to a Pediatric Written Request

BLAs: Subpart E

- Accelerated approval (21 CFR 601.41)  
 Restricted distribution (21 CFR 601.42)

Subpart H

- Approval based on animal studies

- REMS:  MedGuide  
 Communication Plan  
 ETASU  
 MedGuide w/o REMS  
 REMS not required

Comments:

❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (approvals only)	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Public communications (approvals only)	
• Office of Executive Programs (OEP) liaison has been notified of action	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
• Indicate what types (if any) of information were issued	<input type="checkbox"/> None <input checked="" type="checkbox"/> FDA Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)? • If so, specify the type	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<b>CONTENTS OF ACTION PACKAGE</b>	
<b>Officer/Employee List</b>	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (approvals only)	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included

Action Letters	
❖ Copies of all action letters ( <i>including approval letter with final labeling</i> )	Action(s) and date(s) Approval 05/05/17
Labeling	
❖ Package Insert ( <i>write submission/communication date at upper right of first page of PI</i> )	
<ul style="list-style-type: none"> <li>Most recent draft labeling (<i>if it is division-proposed labeling, it should be in track-changes format</i>)</li> </ul>	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> <li>Original applicant-proposed labeling</li> </ul>	<input checked="" type="checkbox"/> Included
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling ( <i>write submission/communication date at upper right of first page of each piece</i> )	<input checked="" type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input type="checkbox"/> None
<ul style="list-style-type: none"> <li>Most-recent draft labeling (<i>if it is division-proposed labeling, it should be in track-changes format</i>)</li> </ul>	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> <li>Original applicant-proposed labeling</li> </ul>	<input checked="" type="checkbox"/> Included
❖ Labels ( <b>full color</b> carton and immediate-container labels) ( <i>write submission/communication date on upper right of first page of each submission</i> )	
<ul style="list-style-type: none"> <li>Most-recent draft labeling</li> </ul>	<input checked="" type="checkbox"/> Included
❖ Proprietary Name <ul style="list-style-type: none"> <li>Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>)</li> <li>Review(s) (<i>indicate date(s)</i>)</li> </ul>	Acceptable/Radicava/09/14/16 Review: 09/01/16
❖ Labeling reviews ( <i>indicate dates of reviews</i> )	RPM: 05/05/17 DMEPA: 01/30/17 DMPP/PLT (DRISK): 04/19/17 OPDP: 04/11/17 Product Quality 01/19/17
Administrative / Regulatory Documents	
❖ RPM Filing Review <sup>4</sup> /Memo of Filing Meeting ( <i>indicate date of each review</i> )	07/26/16
❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	<input checked="" type="checkbox"/> Not a (b)(2)
❖ NDAs/NDA supplements only: Exclusivity Summary ( <i>signed by Division Director</i> )	<input checked="" type="checkbox"/> Completed ( <b>Do not include</b> )
❖ Application Integrity Policy (AIP) Status and Related Documents <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a>	
<ul style="list-style-type: none"> <li>Applicant is on the AIP</li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> <li>This application is on the AIP               <ul style="list-style-type: none"> <li>If yes, Center Director's Exception for Review memo (<i>indicate date</i>)</li> <li>If yes, OC clearance for approval (<i>indicate date of clearance communication</i>)</li> </ul> </li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No  <input type="checkbox"/> Not an AP action

<sup>4</sup> Filing reviews for scientific disciplines are NOT required to be included in the action package.

❖ Pediatrics ( <i>approvals only</i> ) <ul style="list-style-type: none"> <li>Date reviewed by PeRC _____ If PeRC review not necessary, explain: _____</li> </ul>	N/A Orphan Designation
❖ Breakthrough Therapy Designation	<input checked="" type="checkbox"/> N/A
<ul style="list-style-type: none"> <li>Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded)</li> </ul>	
<ul style="list-style-type: none"> <li>CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>)</li> </ul>	
<ul style="list-style-type: none"> <li>CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Rescission Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>)</li> </ul> <p>(<i>completed CDER MPC templates can be found in DARRTS as clinical reviews or on the <a href="#">MPC SharePoint Site</a></i>)</p>	
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, Formal Dispute Resolution Request decisional letters, etc.) ( <i>do not include OPDP letters regarding pre-launch promotional materials as these are non-disclosable; do not include Master File letters; do not include previous action letters, as these are located elsewhere in package</i> )	
❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)	
❖ Minutes of Meetings	
<ul style="list-style-type: none"> <li>If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>)</li> </ul>	<input checked="" type="checkbox"/> N/A or no mtg
<ul style="list-style-type: none"> <li>Pre-NDA/BLA meeting (<i>indicate date of mtg</i>)</li> </ul>	<input checked="" type="checkbox"/> No mtg
<ul style="list-style-type: none"> <li>EOP2 meeting (<i>indicate date of mtg</i>)</li> </ul>	<input checked="" type="checkbox"/> No mtg
<ul style="list-style-type: none"> <li>Mid-cycle Communication (<i>indicate date of mtg</i>)</li> </ul>	<input type="checkbox"/> N/A 12/08/16
<ul style="list-style-type: none"> <li>Late-cycle Meeting (<i>indicate date of mtg</i>)</li> </ul>	<input type="checkbox"/> N/A 01/31/17
<ul style="list-style-type: none"> <li>Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) (<i>indicate dates of mtgs</i>)</li> </ul>	
❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
<ul style="list-style-type: none"> <li>Date(s) of Meeting(s)</li> </ul>	
<b>Decisional and Summary Memos</b>	
❖ Office Director Decisional Memo ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 05/04/17
Division Director Summary Review ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 05/04/17
Cross-Discipline Team Leader Review ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 05/02/17
PMR/PMC Development Templates ( <i>indicate total number</i> )	<input type="checkbox"/> None 5
<b>Clinical</b>	
❖ Clinical Reviews	
<ul style="list-style-type: none"> <li>Clinical Team Leader Review(s) (<i>indicate date for each review</i>)</li> </ul>	<input checked="" type="checkbox"/> No separate review
<ul style="list-style-type: none"> <li>Clinical review(s) (<i>indicate date for each review</i>)</li> </ul>	05/02/17

<ul style="list-style-type: none"> <li>• Social scientist review(s) (if OTC drug) <i>(indicate date for each review)</i></li> </ul>	<input checked="" type="checkbox"/> None
<ul style="list-style-type: none"> <li>❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not <i>(indicate date of review/memo)</i></li> </ul>	See Clinical review
<ul style="list-style-type: none"> <li>❖ Clinical reviews from immunology and other clinical areas/divisions/Centers <i>(indicate date of each review)</i><sup>5</sup></li> </ul>	<input checked="" type="checkbox"/> None
<ul style="list-style-type: none"> <li>❖ Controlled Substance Staff review(s) and Scheduling Recommendation <i>(indicate date of each review)</i></li> </ul>	<input type="checkbox"/> N/A 03/01/17
<ul style="list-style-type: none"> <li>❖ Risk Management <ul style="list-style-type: none"> <li>• REMS Documents and REMS Supporting Document <i>(indicate date(s) of submission(s))</i></li> <li>• REMS Memo(s) and letter(s) <i>(indicate date(s))</i></li> <li>• Risk management review(s) and recommendations (including those by OSE and CSS) <i>(indicate date of each review and indicate location/date if incorporated into another review)</i></li> </ul> </li> </ul>	<input checked="" type="checkbox"/> None
<ul style="list-style-type: none"> <li>❖ OSI Clinical Inspection Review Summary(ies) <i>(include copies of OSI letters to investigators)</i></li> </ul>	02/01/2017
<b>Clinical Microbiology</b> <input type="checkbox"/> None	
<ul style="list-style-type: none"> <li>❖ Clinical Microbiology Team Leader Review(s) <i>(indicate date for each review)</i></li> </ul>	<input type="checkbox"/> No separate review
<ul style="list-style-type: none"> <li> <ul style="list-style-type: none"> <li>Clinical Microbiology Review(s) <i>(indicate date for each review)</i></li> </ul> </li> </ul>	<input checked="" type="checkbox"/> None
<b>Biostatistics</b> <input type="checkbox"/> None	
<ul style="list-style-type: none"> <li>❖ Statistical Division Director Review(s) <i>(indicate date for each review)</i></li> </ul>	<input checked="" type="checkbox"/> No separate review
<ul style="list-style-type: none"> <li> <ul style="list-style-type: none"> <li>Statistical Team Leader Review(s) <i>(indicate date for each review)</i></li> </ul> </li> </ul>	<input checked="" type="checkbox"/> No separate review
<ul style="list-style-type: none"> <li> <ul style="list-style-type: none"> <li>Statistical Review(s) <i>(indicate date for each review)</i></li> </ul> </li> </ul>	01/23/17
<b>Clinical Pharmacology</b> <input type="checkbox"/> None	
<ul style="list-style-type: none"> <li>❖ Clinical Pharmacology Division Director Review(s) <i>(indicate date for each review)</i></li> </ul>	<input checked="" type="checkbox"/> No separate review
<ul style="list-style-type: none"> <li> <ul style="list-style-type: none"> <li>Clinical Pharmacology Team Leader Review(s) <i>(indicate date for each review)</i></li> </ul> </li> </ul>	<input checked="" type="checkbox"/> No separate review
<ul style="list-style-type: none"> <li> <ul style="list-style-type: none"> <li>Clinical Pharmacology review(s) <i>(indicate date for each review)</i></li> </ul> </li> </ul>	<input type="checkbox"/> None 01/25/17
<ul style="list-style-type: none"> <li>❖ OSI Clinical Pharmacology Inspection Review Summary <i>(include copies of OSI letters)</i></li> </ul>	<input checked="" type="checkbox"/> None requested

<sup>5</sup> For Part 3 combination products, all reviews from the reviewing Center(s) should be entered into the official archive (for further instructions, see “Section 508 Compliant Documents: Process for Regulatory Project Managers” located in the CST electronic repository).

<b>Nonclinical</b> <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> No separate review 05/01/17
• Supervisory Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> No separate review 03/31/17
• Pharm/tox review(s), including referenced IND reviews ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 03/27/17
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary ( <i>include copies of OSI letters</i> )	<input checked="" type="checkbox"/> None requested
<b>Product Quality</b> <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews <sup>6</sup>	
• Tertiary review ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
• Secondary review (e.g., Branch Chief) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
• Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 01/19/17
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team ( <i>indicate date of each review</i> )	Microbiology 01/19/17
❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion ( <i>indicate review date</i> )( <i>all original applications and all efficacy supplements that could increase the patient population</i> )	01/19/17
<input type="checkbox"/> Review & FONSI ( <i>indicate date of review</i> )	
<input type="checkbox"/> Review & Environmental Impact Statement ( <i>indicate date of each review</i> )	
❖ Facilities Review/Inspection	
<input checked="" type="checkbox"/> Facilities inspections ( <i>indicate date of recommendation; within one week of taking an approval action, confirm that there is an acceptable recommendation before issuing approval letter</i> ) ( <i>only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)</i> )	<input checked="" type="checkbox"/> Acceptable Re-evaluation date: <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable

<sup>6</sup> Do not include Master File (MF) reviews or communications to MF holders. However, these documents should be made available upon signatory request.

<b>Day of Approval Activities</b>	
❖ For all 505(b)(2) applications: • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)	<input type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity ( <i>Notify CDER OND IO</i> )
• Finalize 505(b)(2) assessment	<input type="checkbox"/> Done
❖ For Breakthrough Therapy (BT) Designated drugs: • Notify the CDER BT Program Manager	<input type="checkbox"/> Done ( <i>Send email to CDER OND IO</i> )
❖ For products that need to be added to the flush list (generally opioids): <a href="#">Flush List</a> • Notify the Division of Online Communications, Office of Communications	<input type="checkbox"/> Done
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	<input checked="" type="checkbox"/> Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	<input checked="" type="checkbox"/> Done
❖ Ensure that proprietary name, if any, and established name are listed in the <i>Application Product Names</i> section of DARRTS, and that the proprietary name is identified as the “preferred” name	<input checked="" type="checkbox"/> Done
❖ Ensure Pediatric Record is accurate	N/A
❖ Send approval email within one business day to CDER-APPROVALS	<input checked="" type="checkbox"/> Done

## Dan, Jack

---

**From:** Dan, Jack  
**Sent:** Wednesday, May 03, 2017 7:14 AM  
**To:** Doug\_Dobak@mt-pharma-us.com  
**Cc:** Daugherty, Susan B (CSO)  
**Subject:** PMC for NDA 209176 Radicava (edaravone)

**Follow Up Flag:** Follow up  
**Flag Status:** Flagged

Good morning Doug san,

The review team is requesting a post-marketing commitment (see below) and a response by COB Thursday, 05/04/17.

As you have conducted very limited investigation of the dose/response of edaravone in ALS, and have not established whether a ceiling of efficacy has been reached, we are requesting a post-marketing commitment to 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.

Please propose dates for the following items by May 4 COB.

Draft Protocol Submission: xx/20  
Final Protocol Submission: xx/20  
Trial Completion: xx/20  
Final Report Submission: xx/20

Best regards,

### Jack Dan, RPh

*Regulatory Health Project Manager*

Center for Drug Evaluation and Research  
Office of Drug Evaluation I  
Division of Neurology Products  
U.S. Food and Drug Administration  
Tel: 240-402-6940

[Jack.Dan@fda.hhs.gov](mailto:Jack.Dan@fda.hhs.gov)



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

JACK DAN  
05/03/2017

## Dan, Jack

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**From:** Dan, Jack  
**Sent:** Tuesday, April 18, 2017 12:11 PM  
**To:** Doug\_Dobak@mt-pharma-us.com  
**Cc:** Daugherty, Susan B (CSO)  
**Subject:** Information request for NDA 209176 Radicava (edaravone)

Dear Doug san,

We have the following nonclinical information request:

Would you please provide, for Study R-217 (the embryofetal development study in rat), the results of a statistical analysis of the relationship between litter size and fetal body weight, to facilitate our evaluation of dose-related effects on fetal weight. If such an analysis has been conducted, you should provide the location of the information in the study report. The sooner you can provide the information, the better.

Best regards,

**Jack Dan, RPh**

*Regulatory Health Project Manager*

Center for Drug Evaluation and Research  
Office of Drug Evaluation I  
Division of Neurology Products  
U.S. Food and Drug Administration  
Tel: 240-402-6940

[Jack.Dan@fda.hhs.gov](mailto:Jack.Dan@fda.hhs.gov)



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

JACK DAN  
04/18/2017

7 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

**Dan, Jack**

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**From:** Doug\_Dobak@mt-pharma-us.com  
**Sent:** Tuesday, March 14, 2017 8:27 AM  
**To:** Dan, Jack  
**Cc:** Daugherty, Susan B (CSO)  
**Subject:** RE: Edaravone IV NDA #209176

Thanks for the consideration and acknowledgement! Be careful out there, we are closed today.

Happy snow day, Doug san

Douglas N Dobak  
VP, Regulatory Affairs & QA  
Mitsubishi Tanabe Development America, Inc.  
525 Washington Blvd.  
Jersey City, NJ 07310  
[Doug\\_Dobak@mt-pharma-us.com](mailto:Doug_Dobak@mt-pharma-us.com)  
Tel: 908-607-1971  
Cell: (b) (6)

---

**From:** Dan, Jack [mailto:Jack.Dan@fda.hhs.gov]  
**Sent:** Tuesday, March 14, 2017 6:55 AM  
**To:** dobak doug/Dobak Doug <Doug\_Dobak@mt-pharma-us.com>  
**Cc:** Daugherty, Susan B (CSO) <Susan.Daugherty@fda.hhs.gov>  
**Subject:** RE: Edaravone IV NDA #209176

Good morning Doug san,

Your proposal for the timing (April 30, 2018) of the severe hepatic impairment study is acceptable.

Best regards,

**Jack Dan, RPh**  
*Regulatory Health Project Manager*

Center for Drug Evaluation and Research  
Office of Drug Evaluation I  
Division of Neurology Products  
U.S. Food and Drug Administration  
Tel: 240-402-6940  
[Jack.Dan@fda.hhs.gov](mailto:Jack.Dan@fda.hhs.gov)



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**From:** [Doug\\_Dobak@mt-pharma-us.com](mailto:Doug_Dobak@mt-pharma-us.com) [[mailto:Doug\\_Dobak@mt-pharma-us.com](mailto:Doug_Dobak@mt-pharma-us.com)]  
**Sent:** Monday, March 13, 2017 1:34 PM  
**To:** Dan, Jack  
**Cc:** Daugherty, Susan B (CSO)  
**Subject:** RE: Edaravone IV NDA #209176

Dear Jack, regarding the below timing counter proposal for the conduct of the severe hepatic impairment study, I had a back and forth with my colleagues in Japan. In short, the overall timeline suggested is acceptable. However, we respectfully request that the "Final Protocol Submission" for this study be revised slightly to April 2018. (b) (4)

(b) (4)  
(b) (4)  
(b) (4) hence, the request for the April 30th final protocol submission date.

We look forward to finalising this PMR timing commitment with the FDA NDA review team as quickly as possible.

Kind Regards, Doug san

Douglas N Dobak  
VP, Regulatory Affairs & QA  
Mitsubishi Tanabe Development America, Inc.  
525 Washington Blvd.  
Jersey City, NJ 07310  
[Doug\\_Dobak@mt-pharma-us.com](mailto:Doug_Dobak@mt-pharma-us.com)  
Tel: 908-607-1971  
Cell: (b) (6)

---

**From:** Dan, Jack [<mailto:Jack.Dan@fda.hhs.gov>]  
**Sent:** Friday, March 10, 2017 1:22 PM  
**To:** dobak doug/Dobak Doug <[Doug\\_Dobak@mt-pharma-us.com](mailto:Doug_Dobak@mt-pharma-us.com)>  
**Cc:** Daugherty, Susan B (CSO) <[Susan.Daugherty@fda.hhs.gov](mailto:Susan.Daugherty@fda.hhs.gov)>  
**Subject:** RE: Edaravone IV NDA #209176

Dear Doug san,

We have the following proposal for the dates for severe hepatic impairment PMR (b) (4)

1. 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>)

Draft Protocol Submission:	10/31/2017
Final Protocol Submission:	12/15/ <del>2018</del> 2017 (April 30 2018)
Trial Completion:	<u>12/15/2020</u> 2019
Final Report Submission:	<u>06/30/2021</u> 2020

---

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

Draft Protocol Submission:	10/31/2017
Final Protocol Submission:	03/31/2018
Trial Completion:	03/31/2019
Final Report Submission:	11/30/2019

---

3. A carcinogenicity study of edaravone, administered by (b) (4) in mouse.

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

---

4. A two-year carcinogenicity study of edaravone, administered by (b) (4), in rat.

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

---

Please confirm receipt of this email and contact me if you have any questions.

**Jack Dan, RPh**

*Regulatory Health Project Manager*

Center for Drug Evaluation and Research

Office of Drug Evaluation I

Division of Neurology Products

U.S. Food and Drug Administration

Tel: 240-402-6940

[Jack.Dan@fda.hhs.gov](mailto:Jack.Dan@fda.hhs.gov)



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**Dan, Jack**

---

**From:** Dan, Jack  
**Sent:** Tuesday, February 14, 2017 2:43 PM  
**To:** Doug\_Dobak@mt-pharma-us.com  
**Cc:** Daugherty, Susan B (CSO)  
**Subject:** Information request for NDA 209176 Radicava (edaravone)

Dear Doug san,

Our Nonclinical Reviewer has the following information request:

There are nonclinical studies for impurities designated (b) (4). Apparently, (b) (4) is actually impurity (b) (4), (b) (4) is actually impurity (b) (4), but it is unclear what (b) (4) (b) (4) are referring to. Could you provide information clarifying the identities of each of these impurities as well as how much of each is present in the actual drug product.

Please confirm receipt of this email and respond by close of business Wednesday, 02/15/17.

Best regards,

**Jack Dan, RPh**  
*Regulatory Health Project Manager*

Center for Drug Evaluation and Research  
Office of Drug Evaluation I  
Division of Neurology Products  
U.S. Food and Drug Administration  
Tel: 240-402-6940

[Jack.Dan@fda.hhs.gov](mailto:Jack.Dan@fda.hhs.gov)



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**Dan, Jack**

---

**From:** Dan, Jack  
**Sent:** Monday, January 30, 2017 2:49 PM  
**To:** Doug\_Dobak@mt-pharma-us.com  
**Cc:** Daugherty, Susan B (CSO)  
**Subject:** Information advice for NDA 209176 Radicava (edaravone)

Dear Doug san,

We have the following information advice for NDA 209176 Radicava (edaravone) from our Label and Labeling Reviewer:

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

**Carton labeling**

1. Revise the strength statement to display the strength per total followed by strength per mL enclosed by parentheses, as depicted below.<sup>b</sup>

30 mg/100 mL (0.3 mg/mL) OR 30 mg/100 mL  
(0.3 mg/mL)

2. Delete the statement [REDACTED] (b) (4) and change to "Injection" to correctly display the dosage form.<sup>c</sup>

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.<sup>d</sup>

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

<sup>c</sup> USP General Chapter<1121> Nomenclature

<sup>d</sup> 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>

Please confirm receipt of this email and contact me if you have any questions.

Best regards,

**Jack Dan, RPh**

*Regulatory Health Project Manager*

Center for Drug Evaluation and Research

Office of Drug Evaluation I

Division of Neurology Products

U.S. Food and Drug Administration

Tel: 240-402-6940

[Jack.Dan@fda.hhs.gov](mailto:Jack.Dan@fda.hhs.gov)



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NDA 209176

**GENERAL ADVICE**

Mitsubishi Tanabe Pharma Corporation (MTPC)  
Attention: Douglas N. Dobak  
Vice President, Regulatory Affairs and Quality Assurance  
525 Washing Blvd, Suite 400  
Jersey City, NJ 07310

Dear Mr. Dobak:

Please refer to your New Drug Application (NDA) dated June 16, 2016 received June 16, 2016, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for MCI-186 (edaravone) Injection, 30 mg/100 mL.

We refer to your response dated January 23, 2017 to our information request dated January 20, 2017. We have reviewed the proposed relabeling and distribution plan and we find it acceptable.

If you have any questions, call Dahlia A. Woody, Regulatory Business Project Manager, at (301) 796-8427.

Sincerely,

Wendy I. Wilson -S

Digitally signed by Wendy I Wilson S  
DN: c=US, o=U S Government, ou=HHS, ou=FDA,  
ou=People, o=9 2342 19200300 100 1 1=1300396790,  
cn=Wendy I Wilson, S  
Date: 2017.01.30 12:11 01 05'00'

Wendy I. Wilson-Lee, Ph.D.  
Branch Chief, Branch 1 (Acting)  
Division of New Drug Products I  
CDER/OPQ/ONDP

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

/s/  
-----

WENDY I WILSON-LEE  
01/30/2017

**Dan, Jack**

---

**From:** Dan, Jack  
**Sent:** Tuesday, January 17, 2017 1:42 PM  
**To:** Doug\_Dobak@mt-pharma-us.com  
**Cc:** Daugherty, Susan B (CSO)  
**Subject:** Information request for NDA 209176 edaravone

Good afternoon Doug san,

Our Clinical Pharmacology reviewer has the following information request:

1. Please clarify which analytical method was used for [REDACTED] (b) (4) and provide validation data for that method.
2. You stated that two different analytical methods (GC-MS and LC-MS/MS) were used for bioanalysis of the previous studies. Please provide cross-validation data for the two bioanalytical methods. If cross validation was not performed, please provide justifications that the PK data generated by these two methods can be pooled together for your population PK analysis, i.e., no impact from the difference in bioanalytical methods.
3. Please also provide a comparison of PK parameters for edaravone and its metabolites from each of the studies that used GC-MS method (Studies MCI186-01, MCI186-10 and MCI-186-E01) versus LC-MS/MS method (Studies MCI186-14 and MCI186-E02), adjusted for the differences in dose/infusion duration.

Please provide your respond by close of business Thursday, 01/19/17.

Best regards,

**Jack Dan, RPh**  
*Regulatory Health Project Manager*

Center for Drug Evaluation and Research  
Office of Drug Evaluation I  
Division of Neurology Products  
U.S. Food and Drug Administration  
Tel: 240-402-6940

[Jack.Dan@fda.hhs.gov](mailto:Jack.Dan@fda.hhs.gov)



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Dan, Jack

**From:** Dan, Jack  
**Sent:** Friday, January 13, 2017 3:42 PM  
**To:** Doug\_Dobak@mt-pharma-us.com  
**Cc:** Daugherty, Susan B (CSO)  
**Subject:** Information Request/Teleconference for NDA 209176 edaravone

Dear Doug san,

Our Clinical Reviewer has the following comments:

I am unable to replicate your AE table (b) (4)

I used the Analysis AE and SL datasets from your ISS section.

Your Safety Set 1 flag + rows also included Study 12 and extension from Study 17. I deleted them. Also note that some of the events are duplicated by subject if it extended between study phases.

Here is the table I generated in the manner I described. These are events where Edaravone > Placebo and also > 2%.

AEBODSYS	AEDECOD	N (E 60mg)	E 60mg %	N (Placebo)	Pbo %
Gastrointestinal disorders	Abdominal pain	4	2	0	0
	Constipation	31	17	30	16
	Dental caries	5	3	0	0
	Dysphagia	37	20	24	13
General disorders and administration site conditions	Gait disturbance	41	22	21	11
Infections and infestations	Periodontitis	5	3	0	0
	Tinea pedis	6	3	4	2
Injury, poisoning and procedural complications	Laceration	6	3	4	2
	Wound	4	2	3	2
Investigations	Glucose urine present	5	3	3	2
Musculoskeletal and connective tissue disorders	Musculoskeletal disorder	18	10	9	5
Nervous system disorders	Dyslalia	6	3	3	2
Respiratory, thoracic and mediastinal disorders	Cough	5	3	3	2
	Dyspnoea	6	3	3	2
	Pneumonia aspiration	7	4	4	2
	Respiratory disorder	7	4	2	1
	Respiratory failure	9	5	7	4
	Upper respiratory tract inflammation	5	3	4	2
Skin and subcutaneous	Eczema	11	6	6	3

tissue disorders	Excessive granulation tissue	6	3	0	0
	Pruritus	9	5	8	4
	Rash	6	3	5	3
	Seborrhoeic dermatitis	4	2	1	.5

Please provide me with instructions on which dataset and variables I should use to generate the incidence of AEs in the placebo controlled portions of your program.

I would like to speak to someone on Tues AM at 9 AM EST if possible so that this issue does not result in undue delay of the review of your application.

Please provide a teleconference number for Tuesday, 1/17/17 at 9 am (Eastern Standard Time) so that we can have a discussion and also confirm receipt of this email.

Best regards,

**Jack Dan, RPh**  
Regulatory Health Project Manager

Center for Drug Evaluation and Research  
Office of Drug Evaluation I  
Division of Neurology Products  
U.S. Food and Drug Administration  
Tel: 240-402-6940

[Jack.Dan@fda.hhs.gov](mailto:Jack.Dan@fda.hhs.gov)



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**Dan, Jack**

---

**From:** Dan, Jack  
**Sent:** Wednesday, January 11, 2017 2:11 PM  
**To:** Doug\_Dobak@mt-pharma-us.com  
**Cc:** Daugherty, Susan B (CSO)  
**Subject:** Information request for NDA 209176 edaravone

Dear Doug san,

We have an additional information request from our Clinical Pharmacology Reviewer for NDA 209176 edaravone:

Please provide the number of patients in your Phase 3 safety dataset who would be classified with impaired renal function based on CLcr (e.g., mild or moderate), and summarize the number of adverse events (with %) for patients with normal renal function vs. Impaired renal function in both drug treatment and placebo groups.

Please respond by the close of business Friday, 1/13/17.

Best regards,

**Jack Dan, RPh**  
*Regulatory Health Project Manager*

Center for Drug Evaluation and Research  
Office of Drug Evaluation I  
Division of Neurology Products  
U.S. Food and Drug Administration  
Tel: 240-402-6940

[Jack.Dan@fda.hhs.gov](mailto:Jack.Dan@fda.hhs.gov)



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**Dan, Jack**

---

**From:** Dan, Jack  
**Sent:** Wednesday, January 11, 2017 1:15 PM  
**To:** Doug\_Dobak@mt-pharma-us.com  
**Cc:** Daugherty, Susan B (CSO)  
**Subject:** Information request for NDA 209176 edaravone

Dear Doug san,

We have the following information request from our Clinical Pharmacology reviewer:

We received the information you submitted on 1/10/2017 pertinent to the ongoing [REDACTED] (b) (4)

1. [REDACTED] (b) (4)
2. [REDACTED]
3. [REDACTED]
4. [REDACTED]

Please reply by close of business Friday, 1/13/17.

Best regards,

**Jack Dan, RPh**  
*Regulatory Health Project Manager*

Center for Drug Evaluation and Research  
Office of Drug Evaluation I  
Division of Neurology Products  
U.S. Food and Drug Administration  
Tel: 240-402-6940

[Jack.Dan@fda.hhs.gov](mailto:Jack.Dan@fda.hhs.gov)



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PIND 126396

**MEETING MINUTES**

Mitsubishi Tanabe Pharma Development America, Inc.  
Attention: Douglas N. Dobak,  
Vice President, Regulatory Affairs and Quality Assurance  
525 Washington Blvd, Suite 400  
Jersey City, New Jersey 07310

Dear Mr. Dobak:

Please refer to your Pre-Investigational New Drug Application (PIND) file for edaravone (MCI-186).

We also refer to the meeting between representatives of your firm and the FDA on December 9, 2015. The purpose of the meeting was to discuss your upcoming NDA submission for edaravone.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Susan Daugherty, Regulatory Project Manager at (301) 796-0878.

Sincerely,

*{See appended electronic signature page}*

Eric Bastings, MD  
Deputy Director  
Division of Neurology Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

Enclosure:  
Meeting Minutes



FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

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**MEMORANDUM OF MEETING MINUTES**

**Meeting Type:** B  
**Meeting Category:** pre-NDA

**Meeting Date and Time:** December 9, 2015 9:00 am  
**Meeting Location:** 10903 New Hampshire Avenue  
White Oak Building #22, Conference Room: 1313  
Silver Spring, Maryland 20903

**Application Number:** PIND 126396  
**Product Name:** edaravone  
**Indication:** amyotrophic lateral sclerosis (ALS)  
**Sponsor/Applicant Name:** Mitsubishi Tanabe Pharma

**Meeting Chair:** Billy Dunn, MD  
**Meeting Recorder:** Susan Daugherty

**FDA ATTENDEES**

Ellis Unger, MD, Director, Office of Drug Evaluation I  
Billy Dunn, MD, Director, Division of Neurology Products (DNP)  
Eric Bastings, MD, Deputy Director, DNP  
Ronald Farkas, MD, PhD, Clinical Team Leader, DNP  
Nicholas Kozauer, MD, Clinical Team Leader, DNP  
Christopher Breder, MD, PhD, Clinical Reviewer, DNP  
Sally Jo Yasuda, MS, PharmD, Safety Team Leader  
Evelyn Mentari, MD, Clinical Safety Reviewer  
Kun Jin, PhD, Biometrics Team Leader, Division of Biostatistics I (DBI)  
Xiangmin Zhang, PhD, Biometrics Reviewer, DBI  
David Hawver, PhD, Acting Nonclinical Supervisor, DNP  
David Carbone, PhD, Nonclinical Reviewer, DNP  
Yuxin Men, DO, PhD, Clinical Pharmacology Team Leader, Division of Clinical Pharmacology I  
Bilal AbuAsal, PhD, Clinical Pharmacology Reviewer, Division of Clinical Pharmacology I  
Atul Bhattarm, PhD, Pharmacometrics Reviewer  
Andrew Papanastsiou, PharmD, Regulatory Health Project Manager  
Jack Dan, RPh, Regulatory Health Project Manager  
Susan Daugherty, Regulatory Health Project Manager  
Katherine Bonson, PhD, Pharmacologist, Controlled Substance Staff  
Danielle Harris, Team Leader, Division of Medication Error Prevention and Analysis (DMEPA)  
Justine Harris, BS, RPh, Safety Evaluator, DMEPA  
Antoine El-Hage, PhD, Pharmacologist, Office of Scientific Investigation

## **EASTERN RESEARCH GROUP ATTENDEES**

Marc Goldstein, Independent Assessor

## **SPONSOR ATTENDEES**

Takeshi Sakata, Global Project Leader, Manager,

Fumihiko Takahashi, Statistics, Assistant Manager, Data Science Department

Partha Banerjee, PhD, RAC, Senior Director, CMC, Regulatory

Koji Takei, Senior Manager, Medical Science, Clinical Research

Joseph M. Palumbo, MD, Vice President, Clinical Research

Audra C. Durio Manager, Regulatory Affairs

Douglas N. Dobak, Vice President, Regulatory Affairs and Quality Assurance

Debra Kirchner, PhD, DAPT, Senior Director, Nonclinical

Beatriz Rocha, MD, PhD, Executive Director, Head Regulatory Affairs Clinical Strategy

Lisa Travis, MS, RAC, Senior Regulatory Manager

David Gan, MD, DrPH, Vice President, Drug Safety

Masayuki Shimada, Manager, Regulatory Affairs

## **1.0 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. Highlights from the pre-IND meeting include:

- The Division encouraged the sponsor to study a higher dose.
- The size of the safety database appears sufficient to support filing.
- Information from the Japanese ischemic stroke program should be included in the NDA submission.
- FDA would consider all available regulatory pathways for approval that might be appropriate, including both full approval and accelerated approval, based on the data submitted.
- Because evidence suggests that [REDACTED] <sup>(b) (4)</sup> is a genotoxic carcinogen, it should be reduced to a level that would result in a daily dose of not more than 10 µg/day.

On October 22, 2015, a Chemistry, Manufacturing, and Controls-only pre-NDA meeting was held. Highlights from that meeting include:

1. FDA agreed that, pending review of the data, stability data obtained from drug product manufactured with drug substance from the (b) (4) site may be used to establish the expiration dating period for the commercial product.
2. Given the safety concern regarding (b) (4) FDA requests an assessment of whether other approaches (b) (4) are feasible.
3. The sponsor was reminded to apply for a USAN name.
4. No agreements for late submissions were made.

## 2. DISCUSSION

### Question 1

During the June 16, 2015 pre-IND meeting, the Sponsor provided a proposal to establish similarity between the Japanese and US ALS populations. The Agency responded by agreeing that the NDA should include evidence supporting the Sponsor's assertion that clinical practice and treatment guidelines related to ALS are similar in both countries; however, the Sponsor was instructed to directly compare the clinical course of ALS patients in Japan (for example from placebo arms) to patients at similar disease stage in published US clinical trials. The Sponsor subsequently performed population pharmacokinetic (PPK) analysis, further supporting a conclusion that Japanese ALS data are representative of the US population. A summary of these analyses and description of the data to be submitted with the NDA are provided in Section 10.2 of this Briefing Package. A full report of these analyses as well as requested PPK analyses and raw datasets will be provided in the NDA.

*Does the Agency agree with this approach?*

#### FDA Response:

The approach appears acceptable. The data and analyses supporting these conclusions should be submitted with the NDA.

*There was no discussion of this response at the meeting.*

### Question 2

The Sponsor believes edaravone has demonstrated efficacy in ALS patients (b) (4) and therefore proposes the following label indication:

(b) (4)

We understand agreement with the proposed indication will evolve during the NDA review. The Sponsor intends to include the above indication in the NDA. Therefore, a discussion of the proposed indication is provided in Section 10.3 of this Briefing Package.

Does the Agency agree [REDACTED] (b) (4)  
[REDACTED]? Will the Agency consider [REDACTED] (b) (4)?

FDA Response:

While discussion of the specific wording of an indication, if your drug is approved, is premature, we would expect the wording to include something similar to “for the treatment of Amyotrophic Lateral Sclerosis.” The nature of the effects of the drug will be described further in the Clinical Trials section of labeling if your drug is approved.

[REDACTED] (b) (4)  
[REDACTED] you should explain that in your NDA.

Meeting Discussion:

[REDACTED] (b) (4)

**Safety**

**Question 3**

At the time of the Pre-IND meeting, the Agency requested the Sponsor include information from the Japanese ischemic stroke program of edaravone in the ALS marketing application, and expressed a particular interest in deaths, serious adverse events (SAEs), discontinuation due to adverse events (AEs) and idiosyncratic AEs (e.g., hypersensitivity/anaphylactic reactions, hepatic and renal dysfunction).

- a. An overview of the non-ALS safety experience will be summarized within the NDA in Module 2.5.5, “Overview of Safety.” Data from the Japanese ischemic stroke population will be provided as an individual report as part of Module 5.3.5.3, “Reports of Analyses of Data from More Than One Study.” This report will be cross-referenced from the Integrated Summary of Safety (ISS) and will contain data from the clinical trial experience in the edaravone-treated stroke population as well as data from post-marketing experience. These data will be presented in an organized manner with hyperlinked, searchable summary tabulations and relevant listings.

Within the same report, the Sponsor also intends to summarize events reported during routine post-marketing pharmacovigilance in Japan for ALS patients.

*Does the Agency agree this is an appropriate location within the NDA for this information?*

**FDA Response:**

Yes, this is an appropriate location in the NDA for that information. We also concur with the approach described in section 10.4 of your briefing package.

b. The Sponsor is performing an assessment of the clinically significant adverse reactions, described in the Japanese local label, across the entire safety database. A general summary of the methodology of this assessment is provided in Section 10.4 of this Briefing Package. This assessment will be included within the same report of the Japanese ischemic stroke population referenced above, as part of Module 5.3.5.3 in the NDA.

*Does the Agency agree this is an appropriate location within the NDA for this information?*

**FDA Response:**

Yes, this is an appropriate location in the NDA for that information. We also concur with the approach described in section 10.4 of your briefing package.

*There was no discussion of this response at the meeting.*

**Question 4**

During the Pre-IND meeting, the FDA encouraged the Sponsor to include a preliminary discussion on the need for risk management actions during the Pre-NDA meeting. The Sponsor's preliminary proposal for Risk Management Actions is provided in Section 10.5 of this Briefing Package. The Sponsor welcomes the Agency's comments on the proposal.

*Based on the preliminary information provided in the Briefing Package, does the Agency agree the proposal may be appropriate?*

**FDA Response:**

We will be able to further comment on the need for and elements of a risk management plan during the course of our review; however, your initial proposal seems reasonable based on our current knowledge.

*There was no discussion of this response at the meeting.*

**Question 5**

The Sponsor is not planning to conduct a thorough QT study. During the Pre-IND meeting, the Division explained a QT study is unlikely to be a filing issue; however, the Division asked the Sponsor to submit available ECG and QT data from previous clinical studies for review. Although cardiac assessments were not included in studies of ALS patients, ECG data are available from studies of healthy volunteers. An external expert will review available cardiac data including non-clinical, clinical and post-marketing reports outside of the US and a Special Report summarizing available data will be provided at the time of NDA filing in Module 5.3.5.3. A description of the data to be provided at the time of NDA filing is provided in Section 10.6 of this Briefing Package.

*Does the Agency agree with the proposal?*

**FDA Response:**

Your proposal appears acceptable. Whether further cardiac evaluation is needed will be a matter of review.

Please include the following with your summary of the cardiac findings in your NDA submission:

- a. A data definition file which describes the contents of the electronic data sets
- b. Electronic data sets as SAS.xpt transport files (in CDISC SDTM format – if possible) and all the SAS codes used for the primary statistical and exposure-response analyses
- c. Please make sure that the ECG raw data set includes at least the following: subject ID, treatment, period, ECG date, ECG time (up to second), nominal day, nominal time, replicate number, heart rate, intervals QT, RR, PR, QRS and QTc (any corrected QT as points in your report, e.g. QTcB, QTcF, QTcI, etc., if there is a specifically calculated adjusting/slope factor, please also include the adjusting/slope factor for QTcI, QTcN, etc.), Lead, and ECG ID (link to waveform files if applicable)
- d. Data set whose QT/QTc values are the average of the above replicates at each nominal time point
- e. Narrative summaries and case report forms for any
  - i. Deaths
  - ii. Serious adverse events
  - iii. Episodes of ventricular tachycardia or fibrillation
  - iv. Episodes of syncope
  - v. Episodes of seizure
  - vi. Adverse events resulting in the subject discontinuing from the study
- f. ECG waveforms to the ECG warehouse ([www.ecgwarehouse.com](http://www.ecgwarehouse.com))
- g. A completed Highlights of Clinical Pharmacology Table (see Attachment 4)

**Meeting Discussion:**

The sponsor said that some of the information requested for Question 5 may not be available. The Division stated that the sponsor should provide the information that is available. It was also noted that concentration-response information would also be useful, particularly given the high concentrations that may have been used in healthy volunteers. The NDA should explicitly state which of the requested information is not available. The Division additionally commented that it would find the clinical trial data most valuable.

**Question 6**

The Sponsor has evaluated the abuse potential of edaravone according to FDA's Draft Guidance for Industry, "Industry Assessment of Abuse Potential of Drugs," and has determined that abuse potential is minimal based on non-clinical data and extensive clinical experiences including clinical trial data and post-marketing information. Therefore, the Sponsor believes that edaravone should not be scheduled and does not plan to conduct a human drug abuse liability study. A summary of the Sponsor's assessment is provided in Section 10.7 of this Briefing Package and a Special Report will be provided in Module 5.3.5.3 of the NDA at the time of NDA filing.

*Does the Agency agree with the Sponsor's approach?*

**FDA Response:**

Insufficient information was submitted in the meeting package to determine whether a human abuse potential study will be required. In order to fully evaluate the abuse-related studies referred to in your summary you should submit the following information as soon as possible:

- a comprehensive receptor binding study of CNS-related sites. In the summary, you only mention evaluating adenosine, opioid, GABA, and NMDA sites.
- full nonclinical protocols and complete data summaries for each drug and dose tested in each of the animal behavioral studies.
- pharmacokinetic data from animal studies showing plasma levels achieved by each dose/route of administration used in the animal abuse-related studies and a comparison to the plasma levels produced by the highest proposed therapeutic dose in humans.
- a complete list of abuse-related adverse events comparing study drug to placebo, separated by Phase 1 and Phase 2/3 studies, by subject and patient population, by drug dose, and by length of treatment with study drug. Do not truncate representation of data by a cut-off percentage.
- a complete list of abuse-related adverse events reported in post-marketing data, separated by disease, dose, and duration of drug administration. Do not truncate representation of data by a cut-off percentage. Abuse-related adverse events include euphoria-type adverse events (euphoria, euphoric mood, elevated mood, mood alteration) and hallucination, with possible sedation or stimulation, as discussed in the 2010 *Guidance for Industry: Assessment of the Abuse Potential of Drugs*.
- information about how misuse, diversion, or theft of edaravone in clinical trials was assessed.

Please note that submission of an Eight Factor Analysis is not necessary; this document is written by the Department of Health and Human Services.

Meeting Discussion:

The CSS staff emphasized the need to follow its recommendations in order to assess the abuse potential of this CNS-active drug.

## Clinical Pharmacology

### Question 7

During the Pre-IND meeting, the Division requested that the Sponsor evaluate the DDI potential of edaravone with major transporters and the induction/inhibition potential of major cytochrome P450 (CYP) enzymes. The Division also directed the Sponsor to characterize CYP enzymes involved in the metabolism of edaravone and to evaluate the effect of hepatic and renal impairment on the exposure of edaravone. By the time of NDA submission, the Sponsor will have completed relevant *in vitro* DDI studies. A summary of these studies is provided in Section 10.8 of this Briefing Package. The Sponsor also plans to conduct (b) (4) studies of edaravone, and the data will be available following market approval.

*Does the Agency agree with this approach?*

FDA Response:

Your approach appears reasonable. You will also need to submit *in vitro* studies characterizing the CYP isozymes involved in the biotransformation of edaravone.

*There was no discussion of this response at the meeting.*

### General Clinical Pharmacology Comments:

- Please provide the clinical pharmacology summary as a review aid in your NDA submission (see attached template).
- Please clarify whether the to-be-marketed formulation in US is the same as that used in pivotal trials in Japan. If they are different, PK bridging information will be needed.
- Please clarify whether any PK data has been obtained from the pivotal efficacy study. If so, it will need to be submitted to the NDA.
- Please submit population pharmacokinetic analyses, models and datasets as outlined below
  - All datasets used for model development and validation should be submitted as a SAS transport files (\*.xpt). A description of each data item should be provided in a Define.pdf file. Any concentrations and/or subjects that have been **excluded from the analysis** should be flagged and maintained in the datasets.
  - Model codes or control streams and output listings should be provided for all major model building steps, e.g., base structural model, covariates models, final model, and validation model. These files should be submitted as ASCII text files with \*.txt extension (e.g.: myfile\_ctl.txt, myfile\_out.txt).

- A model development decision tree and/or table which gives an overview of modeling steps.
- For the population analysis reports we request that you submit, in addition to the standard model diagnostic plots, individual plots for a representative number of subjects. Each individual plot should include observed concentrations, the individual predication line and the population prediction line. In the report, tables should include model parameter names and units. For example, oral clearance should be presented as CL/F (L/h) and not as THETA(1). Also provide in the summary of the report a description of the clinical application of modeling results.
- In terms of where the code and data should be submitted, the following folders can be used as one example for population PK related codes and data. The codes should be submitted under "module5/datasets/poppk/analysis/programs/" folder (such as run1.ctf.txt, run1.lst.txt, plot1.R.txt) with a define pdf file to explain the role of each file and sometimes with a pdf file as the revieweraid.pdf to explain the flow of running the code if necessary. The datasets should be submitted under "module5/datasets/poppk/analysis/datasets/" folder (such as poppk.xpt, pkpd.xpt) with a define pdf file to explain the variables within each data file.

*There was no discussion of these comments at the meeting.*

## Nonclinical

### Question 8

The sponsor respectfully acknowledges and appreciates FDA's advice on (b) (4) levels per International Conference on Harmonization (ICH) M7 during the pre-IND meeting. (b) (4)

For the drug product, the Sponsor monitors (b) (4) during release testing and during stability studies. After careful consideration of FDA's recommendation, analysis of ICH M7, and relevant toxicological data and stability data, the Sponsor proposes to set the specification limit of (b) (4) % for (b) (4) in the drug product. In addition, the Sponsor believes that the risk-benefit of edaravone in ALS patients is favorable. The rationale for proposed specifications is provided in Section 10.9 of this Briefing Package.

*Does the agency agree with this proposal?*

### FDA Response:

The acceptability of the proposed specification limit of (b) (4) % for (b) (4) will be a matter of review. All information intended to support this limit (including copies of published literature) should be submitted for review.

*There was no discussion of this response at the meeting.*

### Question 9

According to ICH S1A Guidance, "The Need for Long-term Rodent Carcinogenicity Studies of Pharmaceuticals," in instances where the life-expectancy in the indicated population is short

(i.e., less than 2 to 3 years), no long-term carcinogenicity studies may be required. In accordance with published literature, patients with ALS live for 2 to 3 years after the diagnosis (i.e. starting point of treatment) on average (see Section 10.10 of this Briefing Package).

Edaravone is known to have no mutagenicity. In addition, neoplastic changes or preneoplastic lesions were not observed in 26-week studies of edaravone in rats and dogs. In addition, life-time assays conducted by the National Cancer Institute (NCI) showed edaravone has no carcinogenic potential when administered orally to mice and rats (see Attachment 5). Therefore, the Sponsor intends to request a waiver from the requirement to conduct long-term carcinogenicity studies of edaravone.

*Does the Agency agree the NDA will be accepted for review in the absence of long-term carcinogenicity studies and that no further studies are required?*

**FDA Response:**

Carcinogenicity studies will be needed for edaravone; however, because of the seriousness of the indication, they may be conducted post-approval.

**Meeting Discussion:**

The sponsor requested clarification of the need for carcinogenicity studies for products indicated for the treatment of ALS, considering that the typical life expectancy following diagnosis is approximately 3 years. The division stated that carcinogenicity studies are required for ALS therapies because, while the average life expectancy is 3-5 years after diagnosis, some patients survive long enough for carcinogenicity to be of concern.

Regarding the NCI-sponsored dietary carcinogenicity study, the division stated that a dietary study may not be adequate to assess the carcinogenic potential of intravenous administration, the proposed clinical route; the adequacy of the study will be a review issue. The division also noted that, if additional carcinogenicity studies are needed, as seems likely based upon preliminary review, they may be conducted post approval. The sponsor should consider the use of an alternative animal model (e.g., a 6-month study in transgenic mouse) and, in the design of the carcinogenicity studies, should take into account feasibility issues based on the proposed clinical route of administration.

**Question 10**

Nearly 300 nonclinical studies of edaravone have been conducted by the Sponsor over the past 30 years. The Sponsor intends to include reports of all of these nonclinical studies in the NDA. However, the Sponsor does not intend to provide written summaries for all of these nonclinical reports. Instead, the Sponsor proposes to present the nonclinical studies in the NDA as follows:

- Nonclinical studies will be grouped as “Primary,” “Supportive,” or “Other.” Primary studies will include pivotal toxicology studies as specified by ICH M3 guidance and pharmacology and absorption, distribution, metabolism, and excretion (ADME) studies which are considered by the Sponsor to be critical to the Regulatory review of the marketing application. Supportive studies are considered

by the Sponsor to provide direct support of the primary studies (e.g., dose range-finding studies). Studies which do not provide safety information to the ALS indication or are not relevant to ALS are deemed to fall under the category of "Other" (e.g., (b) (4)). In all cases, these other studies do not support important ALS findings.

- For the studies classified as "primary" or "supportive" information will be described in both the written summaries (i.e. M2.6.2, 2.6.4 and 2.6.6) and tabulated summaries (i.e. M2.6.3, 2.6.5 and 2.6.7) consistent with ICH M4S Module 2 for presenting nonclinical information.
- For the studies classified as "other," information will be described in brief tabular format in the written summaries (i.e. M2.6.2, 2.6.4 and 2.6.6), where important features of these studies will be included. An example of a proposed tabulation of "Other" studies to be provided in the NDA is included as Attachment 3, along with a complete listing of all nonclinical studies (pharmacology, ADME, and toxicology) conducted by the Sponsor. No description will be prepared in the tabulated summaries (i.e. M2.6.3, 2.6.5 and 2.6.7). The complete reports for all nonclinical studies will be provided in Module 4 of the NDA.

a. *Does the Agency agree that studies categorized as "Other" by the Sponsor may be provided within Module 2.6 of the NDA in tabulated format only?*

b. *Based on the information provided in the Briefing Package, does the Agency agree that the proposed categorization of nonclinical studies as Primary, Supportive and Other is sufficient to enable review of the NDA?*

**FDA Response:**

You should not submit the nonclinical studies categorized as you propose. All nonclinical studies should be submitted to the NDA as described in relevant guidance (cf. *Guidance for Industry - Providing Regulatory Submissions in Electronic Format - Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*, CDER, June 2008; *ICH M4S*, August 2001).

The nonclinical summaries should include descriptions of all studies; the relevance of any particular study will be a matter of review. However, it is certainly acceptable to focus the discussion on the most relevant nonclinical studies.

*There was no discussion of this response at the meeting.*

## **NDA Format**

### **Question 11**

Most clinical studies for edaravone were conducted many years ago, when creation of Study Data Tabulation Model (SDTM) for submission datasets and Analysis Data Model (ADaM) for analysis datasets was not standard practice. Some studies were conducted

before ICH harmonization in 1997, so AEs were not coded with Medical Dictionary for Regulatory Activities (MedDRA).

Based on this situation, the Sponsor will follow FDA guidance on legacy study data by submitting the following in the NDA for the ALS Phase 2 and 3 clinical studies (MCI-186-12, 16, 17, 18 and 19).

- 1) Raw clinical datasets (not SDTM format) as SAS XPORT transport files along with a define.pdf (data definition file), annotated case report form (CRF) and Study Data Reviewer's Guide (SDRG) for each study.
- 2) Analysis datasets (ADS; not ADaM format) as SAS XPORT transport files along with a define.pdf and Analysis Data Reviewer's Guide (ADRG) for each study. The ADRGs provide dataset specifications as well as algorithm and/or programming code for replication of statistical analysis for primary endpoints. These derived ADS datasets are generated from the above Raw datasets.
- 3) ISS datasets as SAS XPORT transport files along with a define.pdf and ADRG. These ISS datasets are generated from the above Analysis datasets for each study.

A CD containing a sample dataset to illustrate conformance to the submission guidance for legacy data will be provided with this pre-NDA Briefing Package.

*Do the Statistical Reviewers agree with this proposal of ALS data submission for the NDA?*

FDA Response:

We have the following comments regarding the datasets you have sent with the briefing package for format:

1. For your Define files, the definition of all column variables and variable codes must be spelled out. For example, in the ADSL file, you have a variable for TRT01P. You will need to explain what this means.
2. Within that column, you have variable codes (controlled terms), "P" and "M". These need to be defined. Categories defined in the controlled term column such as "1" or "2" need to be defined.
3. All results should have their respective units as an adjacent column and the Define file should include the variable name and definition for the units column.
4. Each individual subject should be assigned a single unique identifier (typically designated as USUBJID) across the entire application (e.g., including open-label extensions of the trials).
5. Your Analysis ADSL and Tabulation DM datasets should have only one row for each subject ID. Our review of your ADSL dataset reveals that 22 subject IDs were used in 3 rows and 184 were used in 2 rows.
6. For your ADAE translated database, please explain how you converted the Japanese terms to English lower level terms.

7. The preparation of the adverse event dataset for the ISS should include MedDRA Preferred Terms from a single version of MedDRA. For your ISS ADAE database, please include a column with the verbatim term, as well as all levels of the MedDRA hierarchy, including High Level (HLT) and High Level Group Terms (HLGT).
8. For all rows in datasets with events (e.g., AEs, concomitant medications) include a column variable for duration of the event with an adjoining column with units (e.g., hours, days).

Please refer to Attachment 2: Clinical Safety Requests. We request the use of standard data formats with this NDA. With the NDA submission, please provide a reviewer guide with the location of responses to these requests.

We also have the following additional Biometrics comments regarding your proposed dataset format:

- In the define documents, in addition to the need to define the variables noted above, you will also need to provide an adequate explanation for the variable label, data format decode of categorical and numerical variable(s), and algorithm(s) to derive new variables from raw clinical datasets to analysis datasets.
- In order to enable the traceability in your efficacy analysis datasets and efficacy results, you will need to provide SAS programs, including necessary SAS macro programs, with adequate documentation for the derivations of the analysis datasets from the raw clinical datasets and for the efficacy analyses.
- You will need to include the subject-level population flags for the randomized population and the intent-to-treat population in your efficacy datasets.
- You will need to include a variable for race in the demographic dataset(s).

We strongly encourage you to provide a test submission of a sample of your datasets prior to the submission of your NDA. This process could help to identify and resolve any potential technical issues that could impact the review of your application.

We consulted the eDATA team and will forward any additional comments they may have.

Meeting Discussion:

The Division said that communications with the eDATA team should be sent via Susan Daugherty, Regulatory Project Manager. It was reiterated that a test submission of a sample of sponsor's datasets prior to the submission of an NDA would facilitate the NDA submission process. Information regarding submitting a test submission and working with the eDATA team is located in Attachment 2 under the heading "Electronic Regulatory Submission." Integrated summary of safety datasets must have uniform variable coding for the entire safety population. The Division noted that it needs to be able to understand and work with the data and that the types of

issues identified above could affect the filability of an application if they impact navigability and interpretability of the submission.

Item 10 in Attachment 2 (Clinical Safety Requests) was also discussed regarding availability of datasets. The Division reiterated that the available data should be submitted. (Post-meeting note: As in the response to Question 5, the NDA should explicitly state what data are not available.)

**Question 12**

The NDA will include Phase 3 clinical studies of edaravone in ALS which were conducted outside of the United States. These studies were not conducted under a US IND. At the time the studies were performed, financial disclosure information was not collected from participating clinical investigators. The Sponsor is subsequently exercising due diligence in attempting to obtain financial disclosure from these investigators in accordance with FDA's Guidance for Clinical Investigators, Industry, and FDA Staff, "Financial Disclosure by Clinical Investigators." A description of the Sponsor's efforts to obtain financial disclosure from participating investigators is described in **Section 10.13** of this Briefing Package.

*Does the Agency agree efforts made to obtain financial disclosure from participating clinical investigators are sufficient to enable review of the NDA?*

**FDA Response:**

We agree with your approach to ensuring due diligence in collecting financial disclosures. You should continue this to obtain as many disclosures as possible. This will not prevent us from beginning our NDA review.

Your NDA should document the efforts to obtain those disclosures you were not able to acquire.

*There was no discussion of this response at the meeting.*

**Question 13**

A list of literature references provided in non-ALS Clinical Study Reports (CSRs) will be provided in the NDA. Copies of these literature references will not be included in the NDA; however, they will be made available upon request.

*Does the Agency agree with this proposal?*

**FDA Response:**

If a particular reference is being used as evidence to support the application, that reference should be included in the application. Otherwise, it does not need to be included in the original NDA submission.

Meeting Discussion:

The Division clarified that if a particular reference was critical to the body of substantial evidence, it should be included in the application. Other literature should be available upon request if needed during the review process.

### 3.0 OTHER IMPORTANT INFORMATION

#### Discussion of the Content of a Complete Application

- The content of a complete application was discussed. No agreements were made for late submissions.

All applications are expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application.

- Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. You stated you intend to submit a complete application and therefore, there are no agreements for late submission of application components.
- A preliminary discussion on the need for a REMS was held and it was concluded that a REMS is not needed at this time, however, that may change during the review.

In addition, we note that a chemistry pre-submission meeting was held on October 22, 2015. We refer you to the minutes of that meeting for any additional agreements that may have been reached.

#### PREA Requirements

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because this drug product for this indication has an orphan drug designation, you are exempt from these requirements. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.

### **Prescribing Information**

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 [CFR 201.56\(a\) and \(d\)](#) and [201.57](#) including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) and [PLLR Requirements for Prescribing Information](#) websites including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential in the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of important format items from labeling regulations and guidances.
- FDA’s established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

### **Manufacturing Facilities**

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, “Product name, NDA/BLA 012345, Establishment Information for Form 356h.”

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
1.				
2.				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

### **Office of Scientific Investigations (OSI) Requests**

The Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators who conduct those inspections (Item I and II). This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

The dataset that is requested in Item III below is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of the site level dataset is voluntary and is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.

This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 1, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

#### **I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).**

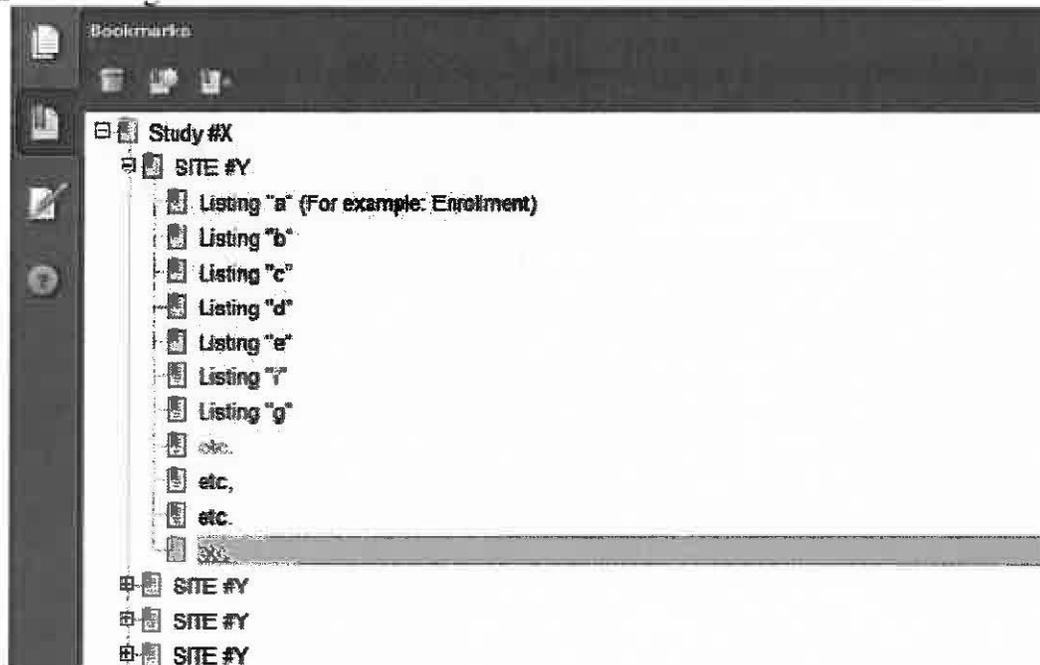
1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:

- a. Site number
  - b. Principal investigator
  - c. Site Location: Address (e.g., Street, City, State, Country) and contact information (i.e., phone, fax, email)
  - d. Location of Principal Investigator: Address (e.g., Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.
2. Please include the following information in a tabular format, *by site*, in the original NDA for each of the completed pivotal clinical trials:
    - a. Number of subjects screened at each site
    - b. Number of subjects randomized at each site
    - c. Number of subjects treated who prematurely discontinued for each site by site
  3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:
    - a. Location at which sponsor trial documentation is maintained (e.g., , monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection
    - b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g., as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.
    - c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.
  4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).
  5. For each pivotal trial provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere in the submission).

## **II. Request for Subject Level Data Listings by Site**

1. For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as "line listings"). For each site, provide line listings for:
  - a. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated

- b. Subject listing for treatment assignment (randomization)
  - c. Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued
  - d. Listing of per protocol subjects/ non-per protocol subjects and reason not per protocol
  - e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
  - f. By subject listing, of AEs, SAEs, deaths and dates
  - g. By subject listing of protocol violations and/or deviations reported in the NDA, including a description of the deviation/violation
  - h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
  - i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
  - j. By subject listing, of testing (e.g., laboratory, ECG) performed for safety monitoring
2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



### III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide a dataset, please refer to the draft Guidance for Industry Providing

**Submissions in Electronic Format – Summary Level Clinical Site Data for CDER’s Inspection Planning” (available at the following link**

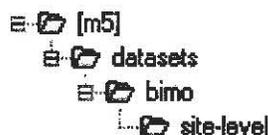
**<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf> ) for the structure and format of this data set.**

**Attachment 1**  
**Technical Instructions:**  
**Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format**

A. Data submitted for OSI review belongs in Module 5 of the eCTD. For items I and II in the chart below, the files should be linked into the Study Tagging File (STF) for each study. Leaf titles for this data should be named “BIMO [list study ID, followed by brief description of file being submitted].” In addition, a BIMO STF should be constructed and placed in Module 5.3.5.4, Other Study reports and related information. The study ID for this STF should be “bimo.” Files for items I, II and III below should be linked into this BIMO STF, using file tags indicated below. The item III site-level dataset filename should be “clinsite.xpt.”

DSI Pre-NDA Request Item <sup>1</sup>	STF File Tag	Used For	Allowable File Formats
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

B. In addition, within the directory structure, the item III site-level dataset should be placed in the M5 folder as follows:



C. It is recommended, but not required, that a Reviewer’s Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be “BIMO Reviewer Guide.” The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

<sup>1</sup> Please see the OSI Pre-NDA/BLA Request document for a full description of requested data files

**References:**

**eCTD Backbone Specification for Study Tagging Files v. 2.6.1**

(<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf>)

**FDA eCTD web page**

(<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm>)

For general help with eCTD submissions: [ESUB@fda.hhs.gov](mailto:ESUB@fda.hhs.gov)

## Attachment 2 Clinical Safety Requests

### Electronic Regulatory Submission:

1. Follow the guidance documents and specifications regarding Electronic Common Technical Document (eCTD) submissions located at the following FDA webpage: [eCTD](#)
2. Refer to the following FDA webpage regarding the electronic submission of regulatory information to CDER: [Electronic Regulatory Submission](#)
3. We request that you submit an eCTD sample for eCTD validation tests. Further instructions are listed at this FDA webpage: [Sample eCTD Submission](#)
4. Send any questions and general information regarding the preparation of submissions in electronic format to [esub@fda.hhs.gov](mailto:esub@fda.hhs.gov)

### Datasets:

5. Refer to the following FDA webpage on [Study Data Standards Resources](#)
6. Follow the following Guidance Documents:
  - a. Providing Regulatory Submissions in Electronic Format-Standardized Study Data
  - b. Study Data Technical Conformance Guide – Technical Specifications Document
    - As outlined in Section 2.2, include a Study Data Reviewer’s Guide in the eCTD Module 5 that describes the use of study data standards and their conformance validation (this is in addition to the Reviewer’s Guide in eCTD Module 1 that provides a high level overview of modules 1 through 5 with hyperlinks).
    - As outlined in Section 4.1, use SDTM data format specifications for clinical tabulations datasets and ADaM for analysis datasets. Analysis datasets should be traceable to the tabulations datasets.
      - As outlined in Section 4.1.1.2, each individual subject should be assigned a single unique identifier across the entire application (e.g., including open label extensions of the trials).
      - As outlined in Section 4.1.4.5, the data definition file, define.xml, should be included to describe the format and content of the submitted SDTM and ADaM datasets.
    - As outlined in Section 6.3.1, the preparation of the adverse event dataset for the ISS should include MedDRA Preferred Terms from a single version of MedDRA. Please specify which version of MedDRA was used.
    - As outlined in Section 8.3.2, specify whether Legacy data has been converted to SDTM formatting. If this is the case, the rationale, methods, and approach to this conversion process will need to be discussed with our data standards team ([eData@fda.hhs.gov](mailto:eData@fda.hhs.gov)). Submit both the original (legacy) and the converted (SDTM) data for these trials. If Legacy data has not been converted to SDTM formatting, provide the rationale.
7. We request that you submit sample standardized datasets (with data definition file) for validation tests and for Division approval prior to submitting the NDA. Further instructions are listed here: [Standardized Data Sample Submission](#)
8. Open CDISC is one possible tool to check for conformance to the CDISC standard.
9. Send any questions regarding the submission or structure of datasets to [eData@fda.hhs.gov](mailto:eData@fda.hhs.gov)
10. Submit datasets for all Phase 1, Phase 2, Phase 3 studies (including open label extension studies), including the Phase 2 and 3 studies performed for indications other than the one proposed for this application.
11. Submit all SAS codes used to create your analyses for the ISE and ISS. If a SAS code contains a macro, please also include the macro code.

**General Submission Contents:**

12. Provide Data Safety Monitoring Board (DSMB) meeting minutes (including any data/slides presented). For those meetings that were cancelled or meetings where no minutes were taken, please include a place holder for that meeting noting such and signed by a member of the clinical team. Please also ensure that these packages come with a table of contents and are bookmarked by date.
13. Include information regarding important regulatory actions in other countries and foreign labeling (translated, if applicable).
14. Submit an annotated version of the pre-NDA meeting minutes that include hyperlinks, when applicable, to the analysis and/or documents requested.
15. Include a copy of each clinical study protocol as well as each amended protocol. Provide a list of the inclusion and exclusion criteria for each of the studies, including those introduced as part of protocol amendments. Please submit all versions of the protocols (and Statistical Analysis Plan) and the date when changes were implemented. Please ensure that a Summary of Changes for each version is included.
16. Include active hyperlinks from the lists of references to the referenced article.
17. Follow the requirements noted in 21CFR 314.50 (d)(5)(vi), Summary of Safety Information and the [Guideline for the Format and Content of the Clinical and Statistical Sections of an Application](#)
18. Provide an assessment of safety as per the [FDA Guidance for Industry: Premarketing Risk Assessment](#)
19. In addition to the comprehensive analyses performed for the pivotal trials, the ISS should also comprehensively integrate safety analyses for all other study group pools for treatment-emergent adverse events (TEAEs), deaths, serious adverse events, discontinuations for TEAEs, TEAEs of special interest, subgroups, and vital sign/laboratory/ECG measurements.
20. Submit a table detailing all of the tables and figures featured in the clinical efficacy and safety sections of the application. The table should contain the following:
  - a. Title of the table or figure in the application
  - b. A hyperlink to the location of the table or figure with page number
  - c. A hyperlink to the SAS code used to create the table or figure (including information regarding the datasets that were used)
21. Format the tables of the ISS according to examples in FDA's [Reviewer Guidance – Conducting a Clinical Safety Review of a New Product Application and Preparing a Report on the Review](#)

**Adverse events:**

1. Follow the coding rules for MedDRA in the ICH-endorsed “MedDRA Term Selection: Points to Consider” document accessible at [MedDRA](#)
2. For each of the studies, the submitted datasets should contain both the verbatim terms and the MedDRA coding with all levels of the MedDRA hierarchy. For each adverse event, MedDRA coding should be provided for the primary MedDRA path as well as the alternative MedDRA coding paths.
3. Provide a summary table of the original AE coding dictionaries that were used in each of the trials.
4. Ensure that all adverse events are presented, and not only events deemed “drug-related.”

5. Provide a table of treatment-emergent adverse events reported in  $\geq 2\%$  of subjects (after rounding) in any drug treated dose group (and greater than placebo) sorted by MedDRA SOC (in alphabetical order) and then by MedDRA Preferred Term.
6. Provide a table which summarizes the outcomes of all pregnancies. Provide a table which summarizes all known adverse events in subject offspring. Include test results for spontaneous and induced abortions.

**Narratives and Case Report Forms (CRFs):**

1. Provide narratives and case report forms for deaths, all discontinuations, SAEs, pregnancies, and AEs of special interest. You should be prepared to supply any additional CRFs or narratives with a rapid turnaround upon request.
2. Include a word file (and excel spreadsheet) that indicates those subjects for whom you submitted a case report form and/or narrative. This file should include an indicator for whether each item was submitted and the reason why it was submitted along with hyperlinks to the case report form and/or narrative.
3. Provide reports for any autopsies conducted during any of the studies.
4. Provide a line listing, narrative, and case report form for all subjects who fit the Hy's Law lab criteria.
5. Note that CRFs should include all clinical documents collected about the patient regardless of whether you label them "CRFs", e.g., Medwatch/CIOMS forms, event fax coversheets, SAE or event worksheets, narrative worksheets, data queries, etc.
6. Provide both narratives and CRFs for all discontinuations (including Lost to follow-up, Other, Physician/investigator decision, Patient decision, Withdrew consent). Provide a tabular listing of all subjects with discontinuations, sorted by reason. The table should include columns for study number, treatment group, unique subject ID, primary reason for discontinuation; for reasons including Lost to follow-up, Other, Physician/investigator decision, Withdrew consent, and Patient decision, provide more specific information regarding the discontinuation.
7. Narrative summaries should provide a complete synthesis of all available clinical data and an informed discussion of the case. The narratives should be comprehensive enough for the reader to come to a reasonable conclusion regarding the subject and the adverse event. The following items should be included (but not limited to):
  - Patient age and gender
  - Adverse event onset and stop dates (presented as relative Study Day number)
  - Signs and symptoms related to the adverse event being discussed
  - An assessment of the relationship of exposure duration to the development of the adverse event
  - Pertinent medical history
  - Concomitant medications with start dates relative to the adverse event
  - Pertinent physical exam findings
  - Any abnormal vital sign measurements
  - Pertinent test results (e.g., lab data, ECG data, biopsy data, autopsy results)
  - Discussion of the diagnosis as supported by available clinical data
  - For events without a definitive diagnosis, a list of the differential diagnoses
  - Treatment provided
  - Re-challenge results (if performed)

- Outcomes and follow-up information

**Laboratory and Vital Sign Measurements:**

1. Refer to the following FDA webpage for the CDER position on use of SI units for lab tests:  
[SI Units](#)
2. Provide the normal reference ranges for every laboratory value.
3. Clearly list the normal values, as well as the thresholds for analysis of outliers, for outlier analyses of laboratory data, vital signs data and ECG data.
4. Provide a table summarizing the frequency of each laboratory test routinely measured during each study in the clinical development program.
5. For laboratory parameters measured routinely in any placebo-controlled study, we request analyses of mean changes, as well as a shift table of change from baseline to worst post-treatment value for the entire placebo-controlled study period. Provide results for the placebo group, each edaravone dose group, as well as for all edaravone dose groups combined. When possible, grade shift changes using CTCAE severity grades. For parameters without CTCAE severity grades, clearly list the severity grading parameters with the shift table. For each analysis, provide the number of subjects analyzed. Provide a list of laboratory parameters analyzed.
6. For laboratory parameters measured routinely in any study, we request analyses of mean changes, as well as a shift table of change from baseline to worst post-treatment value in all edaravone subjects for the entire study period (including extension studies). Provide results for each edaravone dose group, as well as for all edaravone dose groups combined. When possible, grade shift changes using CTCAE severity grades. For parameters without CTCAE severity grades, clearly list the severity grading parameters with the shift table. For each analysis, provide the number of subjects analyzed. Provide a list of laboratory parameters analyzed.
7. Use the latest version of the National Institutes of Health (NIH) Common Terminology Criteria for Adverse Events (CTCAE) for toxicity grades and shift analyses, and indicate the version used.
8. Report the number and percentage of subjects with at least one post-treatment vital sign measurement meeting any of these criteria:
  - Systolic Blood Pressure: <90 mmHg, >140 mmHg, >160 mmHg
  - Diastolic Blood Pressure: <50 mmHg, >90 mmHg, >100 mmHg
  - Pulse Rate: <60 bpm, >100 bpm
  - Body Weight: decrease of  $\geq 7\%$  from baseline and increase of  $\geq 7\%$  from baseline
  - Temperature: >38.0 °C, <36.0 °C
  - Respiratory rate: <12 breaths/min, > 20 breaths/min
9. Summarize the protocols for collecting ECG data. Summarize the frequency of post-treatment QTc >450 ms, >480 ms, and >500 ms.

**Other requests:**

1. Submit individual patient profiles containing all laboratory and other study results in a single place for each patient. Provide this information for patients who died, had a serious adverse event, discontinued from the trial due to an adverse event, or had a medically significant event for which a narrative is submitted. Include all the information recorded for that patient, including but not limited to:
    - Age
    - Sex
    - Dates of screening, randomization and starting therapy
    - Whether the patient completed or did not complete the study, with dates and reason for withdrawal
    - Adverse events ( reported term, preferred term, start and stop date [with relative study day], seriousness, outcome, whether it resolved or not and action taken with drug)
    - Prior medications and concomitant medications with dates of start and end
    - Vital signs and laboratories, sorted by date, with reference ranges \*
    - Full reports for radiologic studies, ECG, MRI, pathology results, and special studies with dates and reference ranges \*
    - Autopsy reports for all deaths. (If an autopsy report is not available, explicitly state this.)
- \* Provide relevant results obtained outside of clinical trial visits, including those obtained during hospitalization or emergency room visits, in each patient file. Also include baseline study results.

Appendix 1: Updated List of MedDRA Search terms for identification of DRESS (MedDRA Version 13.1 – please update PTs with MedDRA version in current application)<sup>2</sup>

*Modified RegiSCAR criteria for DRESS<sup>3</sup>*

Reaction suspected to be drug related with

1. Acute skin rash
2. Involvement of at least one internal organ
3. Enlarged lymph nodes of at least two sites
4. One of the following blood count abnormalities (as reference you should use the limits provided by the lab that has done the analysis)
  - lymphocytes above or below the lab limits
  - eosinophils above the lab limits (in % or absolute count)
  - platelets below the lab limits
5. Fever above 38°C

(At least 3 of these criteria should be present for HSS/DRESS)

Please include events that occurred within 30 days of each other.

Source: <http://regiscar.uni-freiburg.de/diseases/dress/index.html>

## 1. ACUTE SKIN RASH

### Skin and subcutaneous tissue disorders SOC

Dermatitis (any Preferred Term that includes the word dermatitis)  
Drug eruption  
Eczema  
Erythema multiforme  
Erythema nodosum  
Rash (any PT that includes the word rash)  
Skin lesion  
Skin reaction  
Skin exfoliation  
Stevens-Johnson Syndrome  
Toxic epidermal necrolysis  
Toxic skin eruption  
Urticaria

## 2. INVOLVEMENT OF AT LEAST ONE INTERNAL ORGAN

### Blood and lymphatic disorders SOC:

Agranulocytosis  
Aplastic anaemia  
Aplasia pure red cell  
Autoimmune lymphoproliferative syndrome  
Autoimmune neutropenia  
Autoimmune pancytopenia

<sup>2</sup> MedDRA version 13.1. Some PT may be mentioned in more than one SOC.

<sup>3</sup> There should be certain temporal proximity for the onset of these AE (within 1 month of each other).

Blood disorder  
Bone marrow disorder  
Bone marrow failure  
Bone marrow toxicity  
Coagulopathy  
Disseminated intravascular coagulation  
Drug rash with eosinophilia and systemic symptoms  
Eosinophilia  
Febrile neutropenia  
Granulocytopenia  
Hemolytic anemia  
Hemolysis  
Hypereosinophilic syndrome  
Leukemoid reaction  
Leukopenia  
Lymphocytosis  
Lymphopenia  
Leukocytoclastic vasculitis  
Lymphadenitis  
Lymphadenopathy  
Lymphoma  
Monocytosis  
Mononucleosis  
Neutropenia  
Pancytopenia  
Platelet disorder  
Platelet toxicity  
Splinitis  
Splenomegaly  
Splenosis  
Thrombocytopenia

Cardiac disorders SOC

Autoimmune myocarditis  
Cardiomyopathy  
Endocarditis  
Eosinophilic myocarditis  
Myocarditis  
Pericarditis  
Pericardial effusion  
Pericardial disease  
Pleuropericarditis

Endocrine disorders SOC

Adrenalitis  
Autoimmune thyroiditis

Thyroiditis

Eye disorders SOC

Eye allergy  
Eye swelling  
Iritis  
Iridocyclitis  
Optic neuritis  
Retinitis  
Uveitis  
Vitritis  
Scleritis

Gastrointestinal disorders SOC

Allergic colitis  
Colitis  
Eosinophilic colitis  
Eosinophilic esophagitis  
Gastritis  
Gingival edema  
Gingival swelling  
Gingivitis  
Glossitis  
Ileitis  
Mouth ulceration  
Mesenteritis  
Oedema mouth  
Oropharyngeal swelling  
Parotitis  
Pancreatitis  
Periodontitis  
Sialoadenitis  
Stomatitis  
Swollen tongue  
Tongue oedema  
Vasculitis gastrointestinal

Hepatobiliary disorders SOC

Autoimmune hepatitis  
Blood amylase increased  
Blood trypsin increased  
Cholangitis  
Cholecystitis  
Hepatic failure  
Hepatic functional abnormal  
Hepatic encephalopathy

- Hepatic infiltration eosinophilic
- Hepatitis
- Hepatitis acute
- Hepatitis toxic
- Hepatocellular injury
- Hepatomegaly
- Hepatosplenomegaly
- Hepatorenal failure
- Hepatorenal syndrome
- Hepatotoxicity
- Hyperbilirubinaemia
- Hyperlipasaemia
- Jaundice
- Liver disorder
- Lipase abnormal
- Lipase increased
- Oedema due to hepatic disease
- Oedematous pancreatitis
- Pancreatic enzymes increased
- Pancreatic haemorrhage
- Pancreatic necrosis
- Pancreatitis (any PT that includes the word pancreatitis)
- Pancreatorenal syndrome
- Peripancreatic fluid collection
- Swollen tongue

General disorders SOC

- Influenza like illness
- Malaise
- Multiorgan failure

Immune system disorders SOC

- Allergic bronchitis
- Allergic cough
- Allergic cystitis
- Allergic keratitis
- Allergic oedema
- Allergic sinusitis
- Alveolitis allergic
- Anaphylactic reaction
- Anaphylactic shock
- Anaphylactoid reaction
- Asthma
- Angioedema
- Antiphospholipid syndrome
- Autoimmune disorder

Autoimmune hepatitis  
Biliary cirrhosis primary  
Bronchospasm  
Circumoral oedema  
Cholangitis sclerosing  
Dermatomyositis  
Drug hypersensitivity  
Drug induced hypersensitivity  
Encephalitis  
Encephalopathy allergic  
Eyelid oedema  
Eosinophilic fasciitis  
Face oedema  
Hypersensitivity  
Idiopathic thrombocytopenic purpura  
Glomerulonephritis  
Laryngeal oedema  
Lip oedema  
Lip swelling  
Myasthenia Gravis  
Myositis  
Nephrogenic systemic fibrosis  
Oedema mouth  
Panniculitis  
Pemphigus  
Pemphigoid  
Periorbital oedema  
Pruritus allergic  
Polymyositis  
Reaction to drug excipients  
Sarcoidosis  
Serum sickness  
Systemic lupus erythematosus  
Systemic sclerosis  
Type IV hypersensitivity reaction  
Vasculitis (including organ vasculitis: cerebral, GI, renal, retinal, ocular pulmonary, etc)  
Vitiligo

Investigations SOC

***Hematologic***

Any preferred term (PT) that reflects increased, decreased or abnormal MedDRA  
Haematologic investigations High Level Group Term (HLGT)

***Hepatobiliary***

Blood tests increased or abnormal  
Alanine aminotransferase

Amylase  
Aspartate aminotransferase  
Bilirubin conjugated  
Blood amylase  
Blood bilirubin  
Blood bilirubin unconjugated  
Gamma-glutamyltransferase increased  
Lipase  
Liver function test  
Transaminases  
Biopsy liver abnormal

***Immunologic***

Any PT that reflects a positive or abnormal result under MedDRA Immunology and allergy investigations HLG, and Investigations, imaging and histopathology procedures NEC, HLG

***Lung*** Biopsy lung abnormal

***Renal***

Blood creatine increased or abnormal  
Blood urea increased or abnormal  
Creatinine renal clearance decreased  
Glomerular filtration rate decreased  
Blood urine  
Cells in urine  
Eosinophils urine  
Protein urine  
Red blood cells urine  
Urinary casts  
Urinary casts present  
Biopsy kidney abnormal

***Skin*** Biopsy skin abnormal

Musculoskeletal and connective tissue disorders

Arthralgia  
Arthritis  
Arthropathy  
Joint swelling  
Joint warmth  
Lupus-like syndrome  
Myopathy  
Myositis  
Polyarthritis  
Tendonitis

Tenosynovitis  
Synovitis  
Any PT under the MedDRA Connective tissue disorder HLGT.

Neoplasms benign, malignant and unspecified (including cysts and polyps) SOC

Lymphoma (any kind of lymphoma)  
Pseudolymphoma

Nervous system disorders SOC

Acoustic neuritis  
Arachnoiditis  
Central nervous system inflammation  
CNS ventriculitis  
Epiduritis  
Encephalitis (all PTs under Encephalitis NEC, High level term [HLT])  
Encephalopathy  
Leukoencephalitis  
Leukoencephalomyelitis  
Meningitis (all PTs under Meningitis NEC, HLT)  
Myelitis  
Neuritis cranial  
Neuropathy  
Polyneuropathy  
Reye's syndrome  
Toxic optic neuropathy  
Vasculitis cerebral

Renal and urinary disorders SOC

Anuria  
Cardiorenal syndrome  
Dialysis  
Eosinophilic cystitis  
Haematuria  
Haemodialysis  
Haemolytic uraemic syndrome  
Hepatorenal failure  
Hepatorenal syndrome  
Pancreatorenal syndrome  
Peritoneal dialysis  
Oedema due to renal disease  
Renal disorder  
Renal failure  
Renal impairment  
Renal toxicity  
Any PT under MedDRA Nephropathies HLGT

Respiratory, thoracic and mediastinal disorders SOC

Allergic bronchitis  
Acute interstitial pneumonitis  
Asthma  
Allergic granulomatous angiitis  
Alveolitis  
Alveolitis allergic  
Angiolymphoid hyperplasia with Eosinophilia  
Eosinophilic bronchitis  
Eosinophilia myalgia syndrome  
Eosinophilic pneumonia  
Interstitial lung disease  
Pleural effusion  
Pleurisy  
Pleurisy viral  
Pleuropericarditis  
Pneumonitis  
Pulmonary eosinophilia  
Pulmonary vasculitis  
Pulmonary toxicity

Vascular disorders SOC

Arteritis (any PT that includes the word arteritis)  
Capillaritis  
Vasculitis (any Pt that includes the word vasculitis)

**3. ENLARGED LYMPH NODES IN AT LEAST TWO SITES**

Search term: Lymphadenopathy

It may be alone or as part of other PTs: Lymphadenopathy Mediastinal

Paratracheal  
Generalised  
Retroperitoneal  
Vaccination site

Include other PT that could reflect lymphadenopathy:

- Benign lymph node neoplasm
- Lymph node palpable
- Lymph node scan abnormal

**4. ONE OF THE FOLLOWING BLOOD COUNT ABNORMALITIES**

- LYMPHOCYTES ABOVE OR BELOW LAB LIMITS**
- EOSINOPHILS ABOVE THE LAB LIMITS**
- PLATELETS BELOW LAB LIMITS**

*In addition to these, there are multiple potential hematologic manifestations of DRESS that were included under Internal Organ involvement*

**5. FEVER ABOVE 38° C**

- Hyperthermia
- Hyperpyrexia
- Pyrexia
- Febrile bone marrow aplasia (and all PTs that include the word “febrile”)

**References:**

**eCTD Backbone Specification for Study Tagging Files v. 2.6.1**

(<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf>)

**FDA eCTD web page**

(<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm>)

**For general help with eCTD submissions: [ESUB@fda.hhs.gov](mailto:ESUB@fda.hhs.gov)**

## Attachment 3

# CLINICAL PHARMACOLOGY SUMMARY AID

## 1. Goal

The goal of this Aid is to facilitate the creation of an optimal Clinical Pharmacology Summary that summarizes the relevant Clinical Pharmacology findings and focuses sponsor and reviewer on the critical review issues of a submission. To guide sponsors in creating the Clinical Pharmacology Summary in NDA and BLA submissions the Aid provides a generic questionnaire that covers the entire Clinical Pharmacology realm. The aggregate answers provided by sponsors generate the desired Clinical Pharmacology Summary in NDA and BLA submissions. Where needed instructions are added to the questions to clarify what the answers should address. The questions and instructions included in this guide are not intended to be either inclusive of all or exclusive of any questions that specific reviews will address. A special Section of the Clinical Pharmacology Summary should identify and discuss the critical findings and issues and indicate how the unresolved issues are addressed.

The Clinical Pharmacology Summary generated by sponsors is a **stand-alone document**, i.e. the answers to the questions including supporting evidence should be self-sufficient. Appropriate use of complementary tables and figures should be made. The sponsors' answers to the questions should be annotated with links to the detailed information in the study reports and the raw data located in SAS transport files.

## 2. Question Based Review

### 2.1 What are the *in vitro* and *in vivo* Clinical Pharmacology and Biopharmaceutics studies and the clinical studies with PK and/or PD information submitted in the NDA or BLA?

All performed Clinical Pharmacology studies (*in vitro* studies with human biomaterials and *in vivo* studies) and clinical studies with PK and/or PD information along with report numbers should be tabulated. Study titles, objectives, treatments (single or multiple doses, size of the dose/interval), demographics (sex, age, race/ethnicity, body weight, creatinine clearance) and numbers of study participants should be listed. Studies whose results support the label should be marked.

### 2.2 General Attributes of the Drug

**2.2.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product?**

Provide background information on the drug substance (description, chemical name, molecular formula, molecular weight, structure), physical characteristics (Log D, solubility, pKa if applicable). Provide tabular information on the drug products, strengths, quantitative composition of ingredients and lot numbers for all formulations used in all *in vivo* studies and indicate corresponding study report numbers.

**2.2.2 What are the proposed mechanism of action and therapeutic indications?**

**2.2.3 What are the proposed dosages and routes of administration?**

**2.2.4 What drugs (substances, products) indicated for the same indication are approved in the US?**

**2.3 General Clinical Pharmacology**

**2.3.1 What are the design features of the clinical pharmacology and biopharmaceutics studies and the clinical studies used to support dosing or claims?**

Provide a tabular description of the designs, methodology and salient findings of the clinical pharmacology-, dose-ranging-, and pivotal studies and other clinical studies with PK and/or PD information in brief for each indication. Indicate duration of study, subjects' demographics, dose regimens, endpoints (clinical/biomarkers) and study report numbers.

**2.3.2 What is the basis for selecting the response endpoints and how are they measured in clinical pharmacology studies?**

Provide a rationale for the selected clinical endpoints and biomarkers. For biomarkers indicate relationship to effectiveness and safety endpoints.

**2.3.3 Are the active moieties in plasma and clinically relevant tissues appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?**

Indicate circulating active moieties and their plasma and-tissue concentration range after therapeutic doses of the drug of interest. Provide evidence that sensitivity of the assay method(s) used is (are) sufficient to determine apparent terminal t<sub>1/2</sub> and AUC.

## **2.4 Exposure-Response**

### **2.4.1 Does the exposure-response relationship support evidence of effectiveness?**

Describe briefly the method(s) used to determine the exposure-effectiveness relationship from randomized and well controlled trials (RCT) and other appropriate studies. Provide evidence that the exposure-response analysis supports evidence of effectiveness: e.g. a significant slope in the E-R relationship or a clear separation in effectiveness at different drug levels and placebo.

Indicate whether the selected effectiveness endpoints are continuous, categorical or event driven variables. Indicate the number of pooled subjects studied and identify the trials they were enrolled in. Provide the results of the analysis of the dose- and/or concentration-effectiveness relationship. Indicate major covariates (e.g. age, body weight, sex, race/ethnicity, creatinine clearance, disease severity, genetic factors, hormonal status see also 2.6/2.7) impacting the exposure-effectiveness relationship. If not identifiable by commonly known covariates, evaluate different strategies, for example therapeutic drug monitoring, to maximize effectiveness for patients with a sub-therapeutic exposure.

Provide point estimate as well as a measure of the inter-subject variability for applicable. Indicate minimum and maximum effective dose- and concentration levels (major active moieties). Provide evidence that with the proposed regimens clinically meaningful effectiveness is maintained throughout the entire dose interval or alternatively provide evidence that maintenance of effectiveness during the entire dose interval is not important. Indicate the magnitude of the effect at peak and trough concentrations with the tested dose regimens. Indicate steady-state trough and peak plasma concentrations of the major active moieties with the proposed dose regimens. Indicate whether AUC, C<sub>max</sub> or C<sub>min</sub> is more correlated with effectiveness. Show the distribution of the effect size for each dose/concentration level tested.

Justify if an analysis of the exposure-effectiveness relationship was not done.

### **2.4.2 What are the characteristics of the exposure-response relationships for safety?**

Describe briefly the method(s) used to determine the exposure-safety relationship. The analysis should focus on adverse events responsible for discontinuations and other drug related toxicities. Indicate whether the safety endpoints are continuous, categorical or event driven variables. Indicate the number of pooled subjects studied and identify the trials they were enrolled in. Provide the results of the analysis of the dose- and/or concentration-safety relationship. Indicate the major covariates (e.g. age, body weight, sex, race/ethnicity, creatinine clearance, disease severity, genetic factors, hormonal status) impacting the exposure-safety relationship. Provide point estimate as well as a measure of the inter-subject variability for relevant safety endpoints. Indicate magnitude and/or frequency of relevant adverse events at the tested dose/concentration levels. Indicate proportion of subjects with an excessive adverse response. Indicate

whether AUC, C<sub>max</sub> or C<sub>min</sub> is more related to clinically relevant adverse effects. Add information on the maximum tolerated single and multiple dose regimens and the corresponding plasma levels [mean (SD) C<sub>max</sub> and AUC] of the circulating major active moieties.

Justify if an analysis of the exposure-safety relationship was not done.

#### **2.4.3 Does this drug prolong QT/QTc Interval?**

Provide a brief description of the study design, regimens, population and data analysis used. Indicate whether plasma concentrations of the drug and the relevant metabolites and the positive control were measured. Give a rationale for the chosen supra-therapeutic dose regimen. Report the findings on the relationship between dose/concentration and QTc interval. Indicate point estimate and 95% confidence interval for the increase of the QTc- interval at the supra-therapeutic dose level. Discuss the relevance of the findings for safety. Provide support for the appropriateness of the selected supra-therapeutic dose, if applicable. Indicate whether the pharmacokinetics of the drug of interest at supra-therapeutic levels is different from that at therapeutic levels.

#### **2.4.4 Is the dose and dosing regimen selected consistent with the known E-R relationship?**

Provide information on the criteria used to select the dose regimen (doses, dose intervals) used in the RCTs. Indicate the therapeutic dose and/or concentration range for the drug and provide evidence that the proposed dose regimens are optimal given the effectiveness/safety profile of the drug.

### **2.5 What are the PK characteristics of the drug?**

#### **2.5.1 What are the single and multiple dose PK parameters of parent drug and relevant metabolites in healthy adults?**

Briefly describe methods (two-stage and/or population approaches, compartment model dependent or-independent methods) in healthy subjects and in patients with the target disease used to determine the pharmacokinetic parameters of parent drug and relevant metabolites (pharmacologically active or impacting the exposure to parent drug or co-administered drugs). Provide mean, median (SD, CV%) pharmacokinetic parameters of parent drug and relevant metabolites after single doses and multiple doses at steady-state [C<sub>max</sub>, t<sub>max</sub>, AUC, C<sub>max,ss</sub>, C<sub>min,ss</sub>, C<sub>max,ss</sub>/C<sub>min,ss</sub>, t<sub>max,ss</sub>, AUC<sub>0-τ</sub>, CL/F, V/F and t<sub>1/2</sub> (half-life determining accumulation factor), accumulation factor, fluctuation, time to steady-state]. Indicate how attainment of steady-state is determined. Provide evidence for attainment of steady-state.

#### **2.5.2 How does the PK of the drug and its relevant metabolites in healthy adults compare to that in patients with the target disease?**

Compare the pharmacokinetic parameters of the drug of interest and relevant

metabolites in healthy subjects and patients with the target disease. Provide a rationale for observed significant differences between healthy subjects and patients with the target disease.

**2.5.3 What is the inter- and intra-subject variability of the PK parameters in volunteers and patients with the target disease?**

Provide mean/median (SD, coefficient of variation, range within 5% to 95% confidence interval bracket for concentrations) about mean AUC, C<sub>max</sub>, C<sub>min</sub>, CL/F and t<sub>1/2</sub> of the parent drug and relevant metabolites after single doses and at steady-state.

**2.5.4 What are the characteristics of drug absorption?**

Indicate absolute and relative bioavailability, lag time, t<sub>max</sub>, t<sub>max,ss</sub>, C<sub>max</sub>, C<sub>max,ss</sub> and extent of systemic absorption of parent drug and relevant metabolites in healthy subjects and patients with the target disease. Indicate mean (SD) for these parameters.

**2.5.5 What are the characteristics of drug distribution?**

Indicate mean (SD) V/F for the drug of interest in healthy subjects and patients with target disease. Provide mean (SD) blood/ plasma ratio for parent drug in healthy subjects. Briefly describe method and pH- and temperature conditions used for determining plasma protein binding for parent drug and relevant metabolites. Provide mean (SD) values of the plasma protein binding of the drug of interest and relevant metabolites measured over the therapeutic range in healthy subjects and patients with target disease and special populations.

**2.5.6 Does the mass balance study suggest renal or hepatic as the major route of elimination?**

Present total, renal and fecal recoveries as percent of the administered total radioactivity. Indicate the percentage of radioactivity excreted as unchanged parent drug in urine and feces and the percent of radioactivity excreted as metabolites in urine and feces.

**2.5.7 What is the percentage of total radioactivity in plasma identified as parent drug and metabolites?**

Provide identification for  $\geq 90\%$  of the circulating total radioactivity (AUC). If multiple small peaks are present whose individual radioactivity is too small to be assignable to individual metabolites provide an estimate for their contribution to circulating total radioactivity.

**2.5.8 What are the characteristics of drug metabolism?**

Present the metabolic scheme for the drug. Provide an estimate for the contribution of metabolism to the overall elimination of the drug of interest. Indicate mean (SD) values for the non-renal clearance in healthy subjects and patients with the target disease.

Indicate whether active metabolites constitute major circulating moieties and if so how much they contribute to effectiveness and/or whether they affect safety.

**2.5.9 Is there evidence for excretion of parent drug and/or metabolites into bile?**

If appropriate provide *in vitro* and/or *in vivo* evidence suggesting that parent drug and/or metabolites are excreted into bile (*in vitro*: parent drug and/or metabolites are substrates of BCRP, *in vivo*: recovery of unchanged parent drug in mass balance- and absolute bioavailability studies suggest excretion into bile)

**2.5.10 Is there evidence for enterohepatic recirculation for parent and/or metabolites?**

Indicate whether there are secondary peaks and humps in the plasma concentration profile correlating with food intake.

**2.5.11 What are the characteristics of drug excretion in urine?**

Provide an estimate of the contribution of renal excretion to the overall elimination of parent drug in healthy volunteers. Present mean values (SD) for the renal clearance (mL/min or mL/min/1.73m<sup>2</sup>) in healthy subjects and in the target population. Using mean plasma protein binding and renal clearance values in healthy subjects estimate the respective contributions of glomerular filtration and net tubular secretion or re-absorption to renal clearance.

**2.5.12 Based on PK parameters, what is the degree of the proportionality of the dose-concentration relationship?**

Briefly describe the statistical methods used to determine the type of pharmacokinetics of the drug and its relevant metabolites (linearity, dose proportionality, non-linearity, time dependency) in healthy subjects and patients with the target disease. Identify the doses tested after single and multiple dose administrations of the drug of interest and the respective dose normalized mean (SD) C<sub>max</sub> and AUC values in healthy subjects and patients with the target disease. Indicate whether the kinetics of the drug is linear, dose proportionate or nonlinear within the therapeutic range. In case of nonlinear or time dependent pharmacokinetics provide information on the suspected mechanisms involved.

**2.5.13 How do the PK parameters change with time following chronic dosing?**

Indicate whether the mean ratio of AUC<sub>0-τ</sub> at steady-state to AUC after the first dose for the circulating major active moieties deviates statistically significantly from 1.0 in healthy subjects and patients with the target disease. Discuss the relevance of the

findings and indicate whether an adjustment of the dose regimen is required. If the pharmacokinetics of the drug of interest changes with time provide a rationale for the underlying mechanism.

#### **2.5.14 Is there evidence for a circadian rhythm of the PK?**

Indicate whether C<sub>max</sub> and C<sub>min</sub> of the parent drug after the morning and evening dose differ significantly. Discuss the relevance of the findings and whether an adjustment of the dose regimen is required for the drug of interest. Provide a rationale for the underlying mechanism for the observed circadian rhythm of the pharmacokinetics of the drug of interest. Indicate whether the dose regimens in the pivotal studies were adjusted for circadian rhythm.

### **2.6 Intrinsic Factors**

#### **2.6.1 What are the major intrinsic factors responsible for the inter-subject variability in exposure (AUC, C<sub>max</sub>, C<sub>min</sub>) in patients with the target disease and how much of the variability is explained by the identified covariates?**

Provide for all studies investigating the impact of the intrinsic factors (age, sex, body weight, ethnicity/race, renal and hepatic impairment) demographics and number of study subjects, and dose regimens. Provide summaries of the results and indicate intrinsic factors that impact significantly exposure and/or efficacy and safety of the drug of interest. Provide for each major identified covariate an estimate for its contribution to the inter-subject variability and indicate how much of the inter-subject variability is explained by the identified covariates.

Provide mean (SD) parameters for AUC, C<sub>max</sub>, clearance, volume of distribution and t<sub>1/2</sub> for pairs studied (e.g. elderly vs. young, male vs. female, normal body weight vs. obese, race/ethnicity(x) vs. race/ethnicity (y), mild vs. severe target disease)

#### **2.6.2 Based upon what is known about E-R relationships in the target population and their variability, what dosage regimen adjustments are recommended for each group?**

Characterize the populations (age, sex, body weight, ethnicity/race) used to determine the impact of each intrinsic factor on variability in exposure and exposure-response. Indicate for each intrinsic factor whether a dose adjustment (change of dose or dose interval or both) is required or not and provide a rationale for either scenario.

##### **2.6.2.1 Severity of Disease State**

##### **2.6.2.2 Sex**

### **2.6.2.3 Body Weight**

### **2.6.2.4 Elderly**

### **2.6.2.5 Pediatric Patients**

If available provide mean (SD, range) pharmacokinetic parameters, biomarker activity, effectiveness and safety in the pediatric sub-populations (neonates (birth-1 month), infants (1 month- 2 years), children (2-12 years) and adolescents (12- < 16 years) and define the target disease. If no information is available in the pediatric population indicate age groups to be investigated in future studies. Provide a summary stating the rationale for the studies proposed and the endpoints and age groups selected. Include a hyperlink to the development plan of the drug of interest in children.

### **2.6.2.6 Race/Ethnicity**

### **2.6.2.7 Renal Impairment**

Characterize the demographics for each subgroup (normal renal function, mild, moderate and severe renal impairment, on and off dialysis). Indicate mean (SD, range) for creatinine clearance estimated by the Cockcroft-Gaul- and MDRD equations for the stages of renal impairment investigated. Provide arithmetic mean (SD) AUC, C<sub>max</sub> and t<sub>1/2</sub> of parent drug and relevant metabolites in the different sub-groups assessed by 2-stage or population PK approaches. Show regressions including 90% confidence intervals of AUC, C<sub>max</sub> and CL/F on Cl<sub>r</sub> for parent drug and relevant metabolites. If a population approach is used provide evidence supporting that statistical power was sufficient to determine impact of creatinine clearance.

Indicate mean (SD) for total and renal clearance of the drug in the different sub-groups and provide estimates of the contribution of glomerular filtration and net tubular secretion or re-absorption to the renal excretion of the drug of interest. Indicate whether plasma protein binding of the active moieties is significantly altered in renal impairment and whether the change in the unbound fraction is clinically relevant. Indicate whether a dose adjustment (dose or dose interval, or both) is required or not for each of the sub-groups of patients with impaired renal function and provide a rationale for either scenario.

### **2.6.2.8 Hepatic Impairment**

Characterize the demographics for each subgroup (normal hepatic function, mild, moderate and severe hepatic impairment based on Child-Pugh scores). Provide information on arithmetic mean (SD) AUC, C<sub>max</sub>, t<sub>max</sub> and t<sub>1/2</sub> of parent drug and relevant metabolites in the different hepatic function sub-groups assessed by two-stage or population PK approaches. Show regressions including 90% confidence intervals of C<sub>max</sub>, AUC or CL/F on the Child-Pugh score for parent drug and relevant metabolites. Indicate whether plasma protein binding of the active moieties is significantly altered in

hepatic impairment and whether the change in the unbound fraction is clinically relevant. Indicate whether a dose adjustment is required or not for each of the subgroups of patients with impaired hepatic function and provide a rationale for either scenario. If a population approach is used provide evidence supporting that statistical power was sufficient to determine impact of Child-Pugh score.

#### **2.6.2.9 What pregnancy and lactation use information is available?**

#### **2.6.3 Does genetic variation impact exposure and/or response?**

Describe the studies in which DNA samples have been collected. If no DNA samples were collected state so. Include a table with links to the studies in which DNA was analyzed and genomic/genetic information is reported. In the description of these studies include demographics, purpose of DNA analysis (effectiveness, safety, drug metabolism, rule in-out of patients, etc.), rationale for the analysis, procedures for bio-specimen sample collection and DNA isolation, genotyping methods, genotyping results in individual subjects, statistical procedures, genotype-phenotype association analysis and results, interpretation of results, conclusions. If genomic polymorphism impacts either exposure and/or response indicate the measures to be taken to safeguard efficacy and safety of the drug in subjects with varying genotypes. Indicate the contribution of genetic factors to inter-subject variability.

#### **2.6.4 Immunogenicity (NOT applicable to small molecule drugs)**

##### **2.6.4.1 What is the incidence (rate) of the formation of the anti-product antibodies (APA), including the rate of pre-existing antibodies, the rate of APA formation during and after the treatment, time profiles and adequacy of the sampling schedule?**

##### **2.6.4.2 Does the immunogenicity affect the PK and/or PD of the therapeutic protein?**

##### **2.6.4.3 Do the anti-product antibodies have neutralizing activity?**

##### **2.6.4.4 What is the impact of anti-product antibodies on clinical efficacy?**

##### **2.6.4.5 What is the impact of anti-product antibodies on clinical safety?**

Provide information on the incidence of infusion-related reactions, hypersensitivity reactions, and cross-reactivity to endogenous counterparts.

## 2.7 Extrinsic Factors

### 2.7.1 Is there an *in vitro* basis to suspect *in vivo* drug-drug interactions?

Summarize the results of the *in vitro* studies performed with the drug of interest as substrate, inhibitor or inducer of relevant CYP and non-CYP enzymes and transporters. Give rationale for why based on the *in vitro* results an interaction study in humans is required or is not required

### 2.7.2 Is the drug a substrate of CYP enzymes?

Briefly describe the methods used (specific chemicals/antibodies, human recombinant CYP enzymes, human microsomes). Indicate incubate, initial rate conditions, concentration range tested relative to  $K_m$ , controls etc. Provide a summary of the results of the *in vitro* studies investigating the drug of interest as a substrate of CYP 450 and non-CYP 450 enzymes. Provide for each of the relevant enzymes a mean estimate for the % contribution to the metabolism of the drug of interest. Discuss the relevance of the *in vitro* findings for the drug of interest as a substrate for deciding which drug-drug interactions should be or need not be performed in humans. For each situation provide supporting evidence.

### 2.7.3 Is the drug an inhibitor and/or an inducer of enzymes?

Briefly describe the methods used (type and source of liver tissue, concentration range tested for the drug of interest as substrate, inhibitor and inducer, experimental conditions, pre-incubation, probe substrates, positive/negative controls. Provide summary results of the *in vitro* studies with human liver tissues for the drug of interest as a potential inhibitor or inducer of enzymes. Indicate whether the drug is a reversible inhibitor (competitive, non-competitive or un-competitive) or an irreversible inhibitor (mechanism based) and supportive evidence. Provide mean (SD) values for  $K_i$ ,  $IC_{50}$  and  $V_{max}$  for each relevant enzyme and probe substrate. Indicate the anticipated maximum total and unbound concentration of the drug of interest as inhibitor ([I]). Provide the mean (SD) % activity relative to the positive control for the drug of interest as inducer. Discuss the relevance of the *in vitro* findings for the drug of interest as an inhibitor or inducer for deciding which drug-drug interactions should be or need not be performed *in vivo* in humans. If appropriate use the  $[I]/K_i$  ratio as a means to assess the likelihood of an *in vitro* result to be clinically relevant. For each situation provide supporting evidence.

### 2.7.4 Is the drug a substrate, an inhibitor and/or an inducer of transporter processes?

See 2.7.2.2 and 2.7.2.3. The instructions for the interactions of the drug of interest as substrate, inhibitor or inducer of transporters are analogous to those for enzymes.

### 2.7.5 Are there other metabolic/transporter pathways that may be important?

### 2.7.6 What extrinsic factors influence exposure and/or response, and what is

**the impact of any differences in exposure on effectiveness or safety responses?**

Indicate extrinsic factors that impact significantly exposure and/or effectiveness and safety of the drug. Indicate extent of increase or decrease in exposure and/or response caused by extrinsic factors. State whether an adjustment of the dose is or is not required and provide supporting evidence for either case.

**2.7.7 What are the drug-drug interactions?**

Provide a list of the drug-drug interaction studies (PK or PD based mechanism) performed and give a rationale for conducting the listed studies. Indicate the suspected mechanism responsible for the interaction. For each of the *in vivo* studies performed provide a rationale for the design selected (single or multiple dose regimens, randomized/non-randomized cross-over or parallel design for perpetrator and/or victim).

**a) Drug of interest is impacted by co-administered other drugs**

Provide information on the demographics of populations, number of subjects, dose levels, and design of the studies performed in humans. Justify the magnitude of the equivalence interval selected if it is greater than the default interval. Report  $t_{1/2}$ , point estimates and 90% confidence intervals of the geometric mean ratios of AUC and  $C_{max}$  for the drug of interest in the presence and absence of each of the co-administered drugs. Provide a summary statement on the drug interaction liability of the drugs as victim. Indicate whether a dose adjustment is required or not. In either case provide a rationale. Define the required adjusted dose regimens.

**b) Drug of interest impacts other co-administered drugs**

Provide information on the demographics of populations, number of subjects, dose levels, and design of the studies performed in humans. Justify the magnitude of the equivalence interval selected if it is greater than the default interval. Provide a summary statement on the drug interaction liability of the drug as a perpetrator. Report  $t_{1/2}$ , point estimates and 90% confidence intervals of the geometric mean ratios of AUC and  $C_{max}$  for each of the co-administered drugs in the presence and absence of the drug of interest.

**2.7.8 Does the label specify co-administration of another drug?****2.7.9 What other co-medications are likely to be administered to the target population?**

**2.7.10 Is there a known mechanistic basis for pharmacodynamic drug-drug interactions?****2.8 General Biopharmaceutics**

For all *in vivo* studies performed in this section indicate study design, demographics and number of subjects enrolled, and type, composition, strength and lot number of the formulations used. Provide summary results with estimates for mean and inter-subject variability on AUC and C<sub>max</sub> after single and multiple dose administration and peak to trough fluctuation after multiple dose administration.

**IR Product**

**2.8.1 Based on the biopharmaceutics classification system principles, in what class is this drug and formulation? What solubility, permeability and dissolution data support this classification?**

**2.8.2 How is the proposed to-be-marketed formulation linked to the clinical service formulation?**

**2.8.2.1 What are the safety or effectiveness issues, if any, for BE studies that fail to meet the 90% CI using equivalence limits of 80-125%?**

**2.8.2.2 If the formulation does not meet the standard criteria for bioequivalence, what clinical pharmacology and/or safety and efficacy data support the approval of the to-be-marketed product?**

**2.8.3 What is the effect of food on the bioavailability of the drug when administered as solution or as drug product?**

Indicate composition and calories of the food administered, and length of the pre-dose fasting period. State whether the impact of food is on the drug substance or the inactive ingredients of the formulation. Indicate the clinical relevance of findings. Indicate the temporal relationship between drug intake and food intake in the pivotal studies.

**2.8.4 Was the bioequivalence of the different strengths of the to be marketed formulation tested? If so were the strengths bioequivalent or not?**

**2.8.5 If unapproved products or altered approved products were used as active controls, how is BE to the to be marketed product demonstrated? What is the link between the unapproved/altered and to be marketed products?**

**MR product (if an IR is already marketed)**

**2.8.6 What is the bioavailability of the MR product relative to the approved IR product? How does the plasma concentration time profile of the MR**

**formulation compare to that of the IR formulation after single and multiple doses?**

Indicate whether or not the pharmacokinetics of the drug of interest is linear, dose proportional or nonlinear after administration of the MR formulation. Summarize data on C<sub>max</sub>, AUC and C<sub>min</sub> of the IR and MR formulations after a single dose and multiple doses at steady-state. Provide information on the fluctuation factor at steady-state.

**2.8.7 What is evidence that MR formulation *in vivo* consistently shows claimed MR characteristics?**

**2.8.8 What is evidence that MR formulation displays less variability in C<sub>max</sub>, AUC and C<sub>min</sub> than IR formulation?**

**2.8.9 Does the MR product show dose dumping *in vivo*?**

Describe design, demographics and number of subjects participating in the studies performed to determine whether dose dumping occurs with the MR formulation when given in the fed state or when given together with alcohol. Present summaries of results.

**2.8.10 Does ethanol *in vitro* have a dose-dumping effect on the MR product?**

Provide the results of the *in vitro* dissolution testing of the various strengths of the ER product in pH 1.2, 4.5 and 6.8 media containing 0, 5, 10, 20 and 40% alcohol. Discuss any dose dumping observed. If an *in vivo* study was performed report the clinical relevance of the findings.

**2.8.11 Are the MR and IR products marketed simultaneously?**

If the intention is to market both the MR and IR products, indicate how patients are converted from the IR to the MR product and vice versa.

**2.8.12 If the NDA is for an MR formulation of an approved IR product without supportive safety and effectiveness studies, what dosing regimen changes are necessary, if any, in the presence or absence of a PKPD relationship?**

**2.8.13 In the absence of effectiveness and safety data what data support the NDA for a MR formulation of an approved IR product?**

## **2.9 Analytical Section**

### **2.9.1 How are parent drug and relevant metabolites identified and what are the analytical methods used to measure them in plasma and other matrices?**

List all assays used and briefly describe the individual methods.

### **2.9.2 Which metabolites have been selected for analysis and why?**

### **2.9.3 For all moieties measured, is free, bound, or total measured?**

Indicate whether free, bound or total (bound+unbound) concentrations of the drug of interest and relevant metabolites are measured and give a rationale for your selection.

### **2.9.4 What bioanalytical methods are used to assess concentrations of the measured moieties?**

Identify all studies that used a particular assay method. For each assay report indicate the corresponding assay validation report.

### **2.9.5 What is the range of the standard curve? How does it relate to the requirements for clinical studies? What curve fitting techniques were used?**

For each method and analyte provide concentration range of calibration curve and indicate respective concentration range for relevant moieties with therapeutic regimens. Indicate fit type of the calibration curves.

#### **2.9.5.1 What are the lower and upper limits of quantitation?**

For each method and analyte indicate LLOD, LLOQ and ULOQ for undiluted and diluted samples.

#### **2.9.5.2 What are the accuracy, precision, and selectivity at these limits?**

For each method and analyte indicate inter-day and intra-day precision (CV%) and inter-day and intra-day accuracy (RE%).

#### **2.9.5.3 What is the sample stability under conditions used in the study?**

For all studies in which concentrations of the drug of interest and relevant metabolites were measured provide information on initiation date of study, date of last sample analyzed and total sample storage time. For each method and matrix provide information on the stability of the analytes, i.e. number of freeze-thaw cycles, benchtop stability at room temperature and stability during long term storage at  $\leq -20^{\circ}$  C.

#### **2.9.5.4 What is the plan for the QC samples and for the reanalysis of the incurred samples?**

For each study, method and analyte indicate precision (CV%) and accuracy (%RE) using the QC samples measured alongside samples with unknown concentrations. Indicate the concentrations of the QC and incurred samples used.

**2.9.5.5 What evidence is available demonstrating that neither the assay of the drug on interest is impacted by co-administered other drugs and vice versa?**

**Applicable to therapeutic proteins only**

**2.9.5.6 What bioanalytical methods are used to assess therapeutic protein concentrations?**

Briefly describe the methods and summarize the assay performance.

**2.9.5.7 What bioanalytical methods are used to assess the formation of the anti-product antibodies?**

Briefly describe the methods and assay performance including sensitivity, specificity, precision, cut point, interference and matrix, etc.

**2.9.5.8 What is the performance of the neutralizing assay(s)?**

**Attachment 4****Table 1. Highlights of Clinical Pharmacology and Cardiac Safety**

Therapeutic dose and exposure	Include maximum proposed clinical dosing regimen Mean (%CV) Cmax and AUC at the single maximum proposed clinical dose Mean (%CV) Cmax and AUC at the steady state with the maximum proposed clinical dosing regimen	
Maximum tolerated dose	Include if studied or NOAEL dose	
Principal adverse events	Include most common adverse events; dose limiting adverse events	
Maximum dose tested	Single Dose	Specify dose
	Multiple Dose	Specify dosing interval and duration
Exposures Achieved at Maximum Tested Dose	Single Dose	Mean (%CV) Cmax and AUC
	Multiple Dose	Mean (%CV) Cmax and AUC
Range of linear PK	Specify dosing regimen	
Accumulation at steady state	Mean (%CV); specify dosing regimen	
Metabolites	Include listing of all metabolites and activity	
Absorption	Absolute/Relative Bioavailability	Mean (%CV)
	Tmax	<ul style="list-style-type: none"> <li>• Median (range) for parent</li> <li>• Median (range) for metabolites</li> </ul>
Distribution	Vd/F or Vd	Mean (%CV)
	% bound	Mean (%CV)
Elimination	Route	<ul style="list-style-type: none"> <li>• Primary route; percent dose eliminated</li> <li>• Other routes</li> </ul>
	Terminal t <sub>1/2</sub>	<ul style="list-style-type: none"> <li>• Mean (%CV) for parent</li> <li>• Mean (%CV) for metabolites</li> </ul>
	CL/F or CL	Mean (%CV)
Intrinsic Factors	Age	Specify mean changes in Cmax and AUC
	Sex	Specify mean changes in Cmax and AUC
	Race	Specify mean changes in Cmax and AUC
	Hepatic & Renal Impairment	Specify mean changes in Cmax and AUC
Extrinsic Factors	Drug interactions	Include listing of studied DDI studies with mean changes in Cmax and AUC
	Food Effects	Specify mean changes in Cmax and AUC and meal type (i.e., high-fat, standard, low-fat)
Expected High Clinical Exposure Scenario	Describe worst case scenario and expected fold-change in Cmax and AUC. The increase in exposure should be covered by the supra-therapeutic dose.	
Preclinical Cardiac Safety	Summarize <i>in vitro</i> and <i>in vivo</i> results per S7B guidance.	
Clinical Cardiac Safety	Describe total number of clinical trials and number of subjects at different drug exposure levels. Summarize cardiac safety events per ICH E14 guidance (e.g., QT prolongation, syncope, seizures, ventricular arrhythmias, ventricular tachycardia, ventricular fibrillation, flutter, torsade de pointes, or sudden deaths).	

**4.0 ISSUES REQUIRING FURTHER DISCUSSION**

[Identify any issues that remain open at the end of the meeting and require further discussion at a later date. If none exist, please indicate that there were no issues requiring further discussion]

**5.0 ACTION ITEMS**

[Insert any action items that were identify during the meeting. Include who is responsible to complete the action item and the due date. Responsible party should not be an individual, but either sponsor or FDA. Consider the use of a table to present the information]

Action Item/Description	Owner	Due Date
[Insert action item with a brief description, if applicable]	FDA	[Insert date]
[Insert action item with a brief description, if applicable]	Sponsor	[Insert date]

**6.0 ATTACHMENTS AND HANDOUTS**

[Identify any attachments or handouts used during the discussion at the meeting. Generally, a copy of presented slides should be attached. If there are no attachments, insert a comment that there were no attachments or handouts for the meeting minutes.]

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

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ERIC P BASTINGS  
01/07/2016



NDA 209176

**MID-CYCLE COMMUNICATION**

Mitsubishi Tanabe Pharma Development America, Inc.  
Attention: Douglas N. Dobak  
US Agent for Mitsubishi Tanabe Pharma Corporation  
Vice President, Head of Regulatory Affairs and Quality Assurance  
525 Washington Blvd, Suite 400  
Jersey City, NJ 07310

Dear Mr. Dobak:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Radicava (edaravone) injection 30 mg/100 ml.

We also refer to the teleconference between representatives of your firm and the FDA on December 5, 2016. The purpose of the teleconference was to provide you an update on the status of the review of your application.

A record of the teleconference is enclosed for your information.

If you have any questions, call Jack Dan, RPh, Regulatory Project Manager at (240) 402-6940.

Sincerely,

*{See appended electronic signature page}*

Nick Kozauer, MD  
Cross Discipline Team Leader  
Division of Neurology Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

Enclosure:  
Mid-Cycle Communication



FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

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**MID-CYCLE COMMUNICATION**

**Meeting Date and Time:** December 5, 2016 at 2:00 pm

**Application Number:** 209176  
**Product Name:** Radicava (edaravone) 30 mg/100 ml  
**Indication:** Treatment of Amyotrophic Lateral Sclerosis (ALS)  
**Applicant Name:** Mitsubishi Tanabe Pharma Corporation

**Meeting Chair:** Nick Kozauer, MD  
**Meeting Recorder:** Jack Dan, RPh

**FDA ATTENDEES**

Nick Kozauer, MD, Clinical Team Leader, Division of Neurology Products (DNP)  
Wendy Wilson, PhD, Branch Chief (Acting), Drug Product  
Elisa Braver, PhD, Division of Epidemiology I  
Donnella Fitzgerald, PharmD, Division of Risk Management (DRISK) Reviewer  
Dan Berger, PhD, Drug Product Reviewer  
David Carbone, PhD, Nonclinical Reviewer  
Susan Daugherty, Regulatory Project Manager  
Jack Dan, Regulatory Project Manager

**EASTERN RESEARCH GROUP**

Marc Goldstein

**APPLICANT ATTENDEES**

Douglas Dobak- VP RA&QA  
Joe Palumbo MD- VP Medical Sciences  
Koji Takei- Associate Director Medical Sciences  
Rhea Williams-Regulatory Affairs Senior Consultant  
Audra Durio- Manager, Regulatory Affairs  
Hee Young Park MS- Associate Director, Regulatory Affairs  
Ming Ji MD-VP Drug Safety  
Elvia Pariso- Manager, Drug Safety

**1.0 INTRODUCTION**

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are

Mid-Cycle Communication

preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may or may not be able to consider your response before we take an action on your application during this review cycle.

## **2.0 SIGNIFICANT ISSUES**

There are no significant review issues requiring a response from the sponsor at this time.

### **Discussion at the Meeting**

No discussion

## **3.0 INFORMATION REQUESTS**

The clinical IR sent on November 22, 2016, requesting additional information regarding the comparability of ALS in Caucasian and Japanese patients, as well as any comparative efficacy data with edaravone for these populations in other indications is pending.

### **Discussion at the Meeting**

The applicant confirmed that it was planning on submitting the information related to this clinical IR, as requested.

## **4.0 MAJOR SAFETY CONCERNS/RISK MANAGEMENT**

There are no major safety concerns at this time and there are currently no plans for a REMS.

### **Discussion at the Meeting**

No discussion

## **5.0 ADVISORY COMMITTEE MEETING**

We are not currently planning to hold an advisory committee meeting to discuss this application.

### **Discussion at the Meeting**

The Agency confirmed that there was no plan to hold an advisory committee meeting for this application.

## **6.0 LATE-CYCLE MEETING /OTHER PROJECTED MILESTONES**

Late-Cycle Meeting: January 31, 2017

### **Discussion at the Meeting**

The Agency confirmed that the PDUFA goal date for this application is June 16, 2017, based on the required categorization of the application as having a standard review timeline. However, the Agency noted that it always has the ability to expedite reviews for drugs intended to treat serious diseases.

## **6.0 Additional Meeting Discussion**

Mid-Cycle Communication

- The applicant asked for feedback from the plant inspection resulting in a FD-483 and whether the inspection at Onoda, Japan has been scheduled. The Agency noted that it was unable to comment on manufacturing site inspections at this time.
- The Agency commented that the applicant's proposed labeling is under review and that a draft label would be provided once it is available.

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/s/  
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NICHOLAS A KOZAUER  
12/23/2016

**Dan, Jack**

---

**From:** Dan, Jack  
**Sent:** Thursday, December 08, 2016 6:58 AM  
**To:** Doug\_Dobak@mt-pharma-us.com  
**Cc:** Daugherty, Susan B (CSO)  
**Subject:** Information request for NDA 209176 edaravone

Good morning Doug san,

Our Clinical Reviewer has the following information request for NDA 209176 edaravone:

Please clarify the meaning of the variable 'At discontinuation' on the bottom row of the Table 11.4.1.2-1 Summary statistics for ALSFRS-R score (FAS) in the Study report CSR\_Protocol:MCI186-19\_ver.2.0, p 154/550.

Please provide an answer by COB by Friday, 9<sup>th</sup> December.

Please confirm receipt of this email and contact me if you have any questions.

Best regards,

**Jack Dan, RPh**  
*Regulatory Health Project Manager*

Center for Drug Evaluation and Research  
Office of Drug Evaluation I  
Division of Neurology Products  
U.S. Food and Drug Administration  
Tel: 240-402-6940

[Jack.Dan@fda.hhs.gov](mailto:Jack.Dan@fda.hhs.gov)



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## Dan, Jack

---

**From:** Dan, Jack  
**Sent:** Tuesday, December 06, 2016 7:25 AM  
**To:** Doug\_Dobak@mt-pharma-us.com  
**Cc:** Daugherty, Susan B (CSO)  
**Subject:** Information request for NDA 209176 edaravone

Good morning Doug,

Our Clinical Reviewer has the following information request for NDA 209176 edaravone:

Please provide information in narrative form about the 6 subjects who received  $\leq 70\%$  of investigational product in the double blind treatment period (Study 19 Study Report, Table 11.1.1-1. This should include what cycles were missed and the reasons for missing treatment. We note this is listed as being described in the Appendix 16.1.9.3, however the information is not easily extractable in that document.

Provide this information by Dec. 8 close of business.

Best regards,

**Jack Dan, RPh**

*Regulatory Health Project Manager*

Center for Drug Evaluation and Research  
Office of Drug Evaluation I  
Division of Neurology Products  
U.S. Food and Drug Administration  
Tel: 240-402-6940

[Jack.Dan@fda.hhs.gov](mailto:Jack.Dan@fda.hhs.gov)



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/s/  
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JACK DAN  
12/06/2016

**Dan, Jack**

---

**From:** Dan, Jack  
**Sent:** Friday, November 25, 2016 7:32 AM  
**To:** Doug\_Dobak@mt-pharma-us.com  
**Cc:** Daugherty, Susan B (CSO)  
**Subject:** Information request for NDA 209176 edaravone

Dear Doug san,

Our Clinical Reviewer has the following information request for NDA 209176:

Please identify the location in the datasets for study MCI-186-16 where the FAS, EESP, and definite or probable/EESP/2Y population designation may be found in a single column or send a SAS transport dataset with this as a column and the unique subject ID as another.

Please respond by the close of business Tuesday, 11/29/16.

Please confirm receipt of this email and contact me if you have any questions.

Best regards,

**Jack Dan, RPh**

*Regulatory Health Project Manager*

Center for Drug Evaluation and Research  
Office of Drug Evaluation I  
Division of Neurology Products  
U.S. Food and Drug Administration  
Tel: 240-402-6940

[Jack.Dan@fda.hhs.gov](mailto:Jack.Dan@fda.hhs.gov)



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/s/  
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JACK DAN  
11/25/2016

## Dan, Jack

---

**From:** Dan, Jack  
**Sent:** Tuesday, November 22, 2016 12:58 PM  
**To:** Doug\_Dobak@mt-pharma-us.com  
**Cc:** Daugherty, Susan B (CSO)  
**Subject:** Information request for NDA 209176 edaravone

Dear Doug san,

Our Clinical Reviewer has the following information request for NDA 209176 edaravone.

We appreciate that you have provided a summary in the Summary of Clinical Efficacy section 2.7.3.4 of the comparison between Japanese and Caucasian patients with respect to

- Diagnostic and evaluative criteria
- Course of natural history
- PK of edaravone

Please provide the review team with the location in your application or provide information on the following areas related to the topic comparing the Japanese and Caucasian populations, particularly those patients with ALS:

- Comparisons of biomarkers relevant to ALS
- Similarities or differences in pharmacodynamics or safety assessments to edaravone in any indication or segment of these ethnic groups.

Please send your completed response by December 15<sup>th</sup>, 2016.

Please confirm receipt of this email and contact me if you have any questions.

Best regards,

**Jack Dan, RPh**

*Regulatory Health Project Manager*

Center for Drug Evaluation and Research  
Office of Drug Evaluation I  
Division of Neurology Products  
U.S. Food and Drug Administration  
Tel: 240-402-6940

[Jack.Dan@fda.hhs.gov](mailto:Jack.Dan@fda.hhs.gov)



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/s/  
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JACK DAN  
11/22/2016

**Dan, Jack**

---

**From:** Dan, Jack  
**Sent:** Tuesday, October 25, 2016 10:43 AM  
**To:** Doug\_Dobak@mt-pharma-us.com  
**Cc:** Daugherty, Susan B (CSO)  
**Subject:** Information request for NDA 209176 edaravone

Good morning Doug san,

Our Clinical Pharmacology review has the following information request for NDA 209176 edaravone:

Please submit PK concentration dataset and subject treatment dataset in SAS XPT format for Study MCI-186-E02. Digital ECGs with annotations from the study in XML format should be uploaded to ECG warehouse ([www.ecgwarehouse.com](http://www.ecgwarehouse.com)).

Please confirm receipt of this email and contact me if you have any questions.

Best regards,

**Jack Dan, RPh**

*Regulatory Health Project Manager*

Center for Drug Evaluation and Research  
Office of Drug Evaluation I  
Division of Neurology Products  
U.S. Food and Drug Administration  
Tel: 240-402-6940

[Jack.Dan@fda.hhs.gov](mailto:Jack.Dan@fda.hhs.gov)



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NDA 209176

**PROPRIETARY NAME REQUEST  
CONDITIONALLY ACCEPTABLE**

Mitsubishi Tanabe Pharma Corporation  
c/o Mitsubishi Tanabe Pharma Development America, Inc.,  
525 Washington Blvd, Suite 400  
Jersey City, NJ 07310

ATTENTION: Douglas N. Dobak  
Vice President, Head of Regulatory Affairs and Quality Assurance

Dear Mr. Dobak:

Please refer to your New Drug Application (NDA) dated and received June 16, 2016, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Edaravone Injection, 30 mg/100 mL.

We also refer to your correspondence, dated and received July 5, 2016, requesting review of your proposed proprietary name, Radicava.

We have completed our review of the proposed proprietary name, Radicava and have concluded that it is conditionally acceptable.

If any of the proposed product characteristics as stated in your above submission(s) are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review. Additionally, if your application receives a complete response, a new request for name review for your proposed name should be submitted when you respond to the application deficiencies.

If you require information on submitting requests for proprietary name review or PDUFA performance goals associated with proprietary name reviews, we refer you to the following:

- Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names  
(<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf>)
- PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 through 2017,  
(<http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf>)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Corwin Howard, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at 240-402-8654. For any other information regarding this application, contact Jack Dan, Regulatory Project Manager in the Office of New Drugs, at 240-402-6940.

Sincerely,

*{See appended electronic signature page}*

Todd Bridges, RPh  
Director  
Division of Medication Error Prevention and Analysis  
Office of Medication Error Prevention and Risk Management  
Office of Surveillance and Epidemiology  
Center for Drug Evaluation and Research

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/s/  
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CORWIN D HOWARD

09/14/2016

LUBNA A MERCHANT on behalf of TODD D BRIDGES

09/14/2016



NDA 209176

**FILING COMMUNICATION –  
NO FILING REVIEW ISSUES IDENTIFIED**

Mitsubishi Tanabe Pharma Development America, Inc.  
Attention: Douglas N. Dobak  
US Agent for Mitsubishi Tanabe Pharma Corporation  
Vice President, Head of Regulatory Affairs and Quality Assurance  
525 Washington Boulevard, Suite 400  
Jersey City, NJ 07310

Dear Mr. Dobak:

Please refer to your New Drug Application (NDA) dated June 16, 2016, received June 16, 2016, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Radicava (edaravone) injection 30 mg/100 ml.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is June 16, 2017. This application is also subject to the provisions of “the Program” under the Prescription Drug User Fee Act (PDUFA) V (refer to <http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm>).

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any post marketing commitment requests by May 26, 2017.

In addition, the planned date for our internal mid-cycle review meeting is November 15, 2016. We are not currently planning to hold an advisory committee meeting to discuss this application.

We request that you submit the following information:

1. Tables summarizing what vital signs are available from other edaravone studies, the title/number of the study reports that summarize those findings, and whether electronic datasets are available and in what format.
2. The NONMEM code for population PK analysis as a stand-alone file.
3. The bioanalytical reports for Studies MCI-186-01 and MCI-186-E01.

### **PRESCRIBING INFORMATION**

Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 [CFR 201.56\(a\) and \(d\)](#) and [201.57](#). As you develop your proposed PI, we encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) and [PLLR Requirements for Prescribing Information](#) websites including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information in the PI on pregnancy, lactation, and females and males of reproductive potential
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of important format items from labeling regulations and guidances and
- FDA’s established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

During our preliminary review of your submitted labeling, we have identified the following labeling issues and have the following labeling comments:

1. Include the Product Title in Highlights (HL) as stated in and required by 21 CFR 201.57(a)(2).
2. 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. Please include a cross-reference under Adverse Reactions.
3. The following heading “FULL PRESCRIBING INFORMATION” must be bolded, must appear at the beginning of the FPI, and should be in UPPERCASE.
4. 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)*].”
5. The DRUG INTERACTIONS section must contain a description of clinically significant interactions. The CLINICAL PHARMACOLOGY section is the appropriate location for information related to drug interaction studies that conclude there is no clinically significant interaction.

6. Under the Risk Summary heading in the Pregnancy subsection, information about the background risk of major birth defects and miscarriage in the U.S. general population must be included, e.g., “In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.”
7. At the end of the Risk Summary heading in the Lactation subsection, include the following statement: “The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for (name of drug) and any potential adverse effects on the breastfed infant from (name of drug) or from the underlying maternal condition.”
8. Under the Risk Summary headings in the Pregnancy and Lactation subsections, include a cross-reference to additional details in the respective Data headings, when applicable. All pertinent details are discussed under the Data headings (i.e., do not include a cross-reference to the NONCLINICAL TOXICOLOGY section).
9. See 21 CFR 201.57(c)(9)(v)(B)(2) for Geriatric Use statements. Please revise to include the number of patients over the age of 75.
10. Please remove the (b) (4)  


We request that you resubmit labeling (in Microsoft Word format) that addresses these issues by September 16, 2016. The resubmitted labeling will be used for further labeling discussions. Use the SRPI checklist to correct any formatting errors to ensure conformance with the format items in regulations and guidances.

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

If you have any questions, call Jack Dan, RPh, Regulatory Project Manager, at (240) 402-6940.

Sincerely,

*{See appended electronic signature page}*

Billy Dunn, MD  
Director  
Division of Neurology Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

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/s/  
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WILLIAM H Dunn  
08/25/2016

**Dan, Jack**

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**From:** Dan, Jack  
**Sent:** Monday, August 15, 2016 1:20 PM  
**To:** Doug\_Dobak@mt-pharma-us.com  
**Cc:** Daugherty, Susan B (CSO)  
**Subject:** Information request for NDA 209176 edaravone

Dear Mr. Dobak,

We have the following information request for NDA 209176 edaravone.

***Please provide the contact information for the contract research organizations (CROs) who were primarily responsible for overall study monitoring for MCI-186-16 and MCI-186-19. Please provide the contact name, address, phone number, fax number, email for these CROs. Also, if located elsewhere, please provide the address where the study records are currently located.***

***Please respond by the close of business (COB) Wednesday, 08/17/16 and follow-up with a submission to the NDA.***

Contact me if you have any questions and please confirm receipt of this email.

Best regards,

Jack Dan, RPh  
Regulatory Project Manager  
Food and Drug Administration  
Office of Drug Evaluation I - Division of Neurology Products  
10903 New Hampshire Avenue  
Building 22, Room 4209  
Silver Spring, MD 20993-0002  
Office: (240) 402-6940  
Fax: (301)796-9842  
Email: [Jack.Dan@fda.hhs.gov](mailto:Jack.Dan@fda.hhs.gov)

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**Dan, Jack**

---

**From:** Dan, Jack  
**Sent:** Wednesday, August 03, 2016 1:46 PM  
**To:** Doug\_Dobak@mt-pharma-us.com  
**Cc:** Daugherty, Susan B (CSO)  
**Subject:** Information request for NDA 209176 edaravone

Dear Mr. Dobak

We have the following information request for NDA 209176 edaravone for the treatment of ALS.

*We refer to your NDA 209176 for edaravone intravenous solution, submitted June 16, 2016. To better inform our review of your proposed carton labeling, container labels, and primary packaging, please submit the following:*

- 1. 3 samples of the proposed edaravone intravenous solution in the intend-to-market packaging.*

*Please submit the above request to the agency by COB Friday, August 12, 2016.*

Please confirm receipt of this email and contact me if you have any questions.

Best regards,

Jack Dan, RPh  
Regulatory Project Manager  
Food and Drug Administration  
Office of Drug Evaluation I - Division of Neurology Products  
10903 New Hampshire Avenue  
Building 22, Room 4209  
Silver Spring, MD 20993-0002  
Office: (240) 402-6940  
Fax: (301)796-9842  
Email: [Jack.Dan@fda.hhs.gov](mailto:Jack.Dan@fda.hhs.gov)

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**Dan, Jack**

---

**From:** Dan, Jack  
**Sent:** Friday, July 15, 2016 7:50 AM  
**To:** Doug\_Dobak@mt-pharma-us.com  
**Cc:** Daugherty, Susan B (CSO)  
**Subject:** ClinPharm Information request for NDA 209176 edaravone

Good morning Mr. Dobak,

Our clinical pharmacology reviewer has the following information request for NDA 209176 edaravone for the treatment of ALS.

*Please submit the NONMEM code for population PK analysis as a stand-alone file.  
Please submit the bioanalytical reports for Studies MCI-186-01 and MCI-186-E01.*

Please send this information by July 21, 2016.

Please confirm receipt of this email and contact me if you have any questions.

Best regards,

Jack Dan, RPh  
Regulatory Project Manager  
Food and Drug Administration  
Office of Drug Evaluation I - Division of Neurology Products  
10903 New Hampshire Avenue  
Building 22, Room 4209  
Silver Spring, MD 20993-0002  
Office: (240) 402-6940  
Fax: (301)796-9842  
Email: [Jack.Dan@fda.hhs.gov](mailto:Jack.Dan@fda.hhs.gov)

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## Dan, Jack

---

**From:** Dan, Jack  
**Sent:** Thursday, July 14, 2016 2:10 PM  
**To:** Doug\_Dobak@mt-pharma-us.com  
**Cc:** Daugherty, Susan B (CSO)  
**Subject:** Information request for NDA 209176 edaravone

Good afternoon Mr. Dobak,

Our reviewer has the following information request for NDA 209176 edaravone for the treatment of ALS:

You note that vital signs were not performed in the ALS studies. Please submit a table summarizing what vital signs are available from other edaravone studies, the title/number of the study reports that summarize those findings, and whether electronic datasets are available and in what format.

Please send this information by 20 July.

Please confirm receipt of this email and contact me if you have any questions.

Best regards,

Jack Dan, RPh  
Regulatory Project Manager  
Food and Drug Administration  
Office of Drug Evaluation I - Division of Neurology Products  
10903 New Hampshire Avenue  
Building 22, Room 4209  
Silver Spring, MD 20993-0002  
Office: (240) 402-6940  
Fax: (301)796-9842  
Email: [Jack.Dan@fda.hhs.gov](mailto:Jack.Dan@fda.hhs.gov)

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/s/  
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JACK DAN  
07/14/2016

**Dan, Jack**

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**From:** Dan, Jack  
**Sent:** Monday, July 11, 2016 8:33 AM  
**To:** Doug\_Dobak@mt-pharma-us.com  
**Cc:** Daugherty, Susan B (CSO)  
**Subject:** Highlights of ClinPharm and Cardiac Safety Table for NDA 209176  
**Attachments:** Highlights of ClinPharm and Cardiac Safety\_20150923.doc

Dear Dr. Dobak,

Our reviewer has the following request for NDA 209176 edaravone. Attached is the Highlights of Clinical Pharmacology and Cardiac Safety table. Please complete the table and send it back as soon as possible. Contact me if you have any questions.

Best regards,

Jack Dan, RPh  
Regulatory Project Manager  
Food and Drug Administration  
Office of Drug Evaluation I - Division of Neurology Products  
10903 New Hampshire Avenue  
Building 22, Room 4209  
Silver Spring, MD 20993-0002  
Office: (240) 402-6940  
Fax: (301)796-9842  
Email: [Jack.Dan@fda.hhs.gov](mailto:Jack.Dan@fda.hhs.gov)

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**Table 1. Highlights of Clinical Pharmacology and Cardiac Safety**

Therapeutic dose and exposure	Include maximum proposed clinical dosing regimen Mean (%CV) C <sub>max</sub> and AUC at the single maximum proposed clinical dose Mean (%CV) C <sub>max</sub> and AUC at the steady state with the maximum proposed clinical dosing regimen	
Maximum tolerated dose	Include if studied or NOAEL dose	
Principal adverse events	Include most common adverse events; dose limiting adverse events	
Maximum dose tested	Single Dose	Specify dose
	Multiple Dose	Specify dosing interval and duration
Exposures Achieved at Maximum Tested Dose	Single Dose	Mean (%CV) C <sub>max</sub> and AUC
	Multiple Dose	Mean (%CV) C <sub>max</sub> and AUC
Range of linear PK	Specify dosing regimen	
Accumulation at steady state	Mean (%CV); specify dosing regimen	
Metabolites	Include listing of all metabolites and activity	
Absorption	Absolute/Relative Bioavailability	Mean (%CV)
	T <sub>max</sub>	<ul style="list-style-type: none"> <li>• Median (range) for parent</li> <li>• Median (range) for metabolites</li> </ul>
Distribution	V <sub>d</sub> /F or V <sub>d</sub>	Mean (%CV)
	% bound	Mean (%CV)
Elimination	Route	<ul style="list-style-type: none"> <li>• Primary route; percent dose eliminated</li> <li>• Other routes</li> </ul>
	Terminal t <sub>1/2</sub>	<ul style="list-style-type: none"> <li>• Mean (%CV) for parent</li> <li>• Mean (%CV) for metabolites</li> </ul>
	CL/F or CL	Mean (%CV)
Intrinsic Factors	Age	Specify mean changes in C <sub>max</sub> and AUC
	Sex	Specify mean changes in C <sub>max</sub> and AUC
	Race	Specify mean changes in C <sub>max</sub> and AUC
	Hepatic & Renal Impairment	Specify mean changes in C <sub>max</sub> and AUC
Extrinsic Factors	Drug interactions	Include listing of studied DDI studies with mean changes in C <sub>max</sub> and AUC
	Food Effects	Specify mean changes in C <sub>max</sub> and AUC and meal type (i.e., high-fat, standard, low-fat)
Expected High Clinical Exposure Scenario	Describe worst case scenario and expected fold-change in C <sub>max</sub> and AUC. The increase in exposure should be covered by the supra-therapeutic dose.	
Preclinical Cardiac Safety	Summarize <i>in vitro</i> and <i>in vivo</i> results per S7B guidance.	
Clinical Cardiac Safety	Describe total number of clinical trials and number of subjects at different drug exposure levels. Summarize cardiac safety events per ICH E14 guidance (e.g., QT prolongation, syncope, seizures, ventricular arrhythmias, ventricular tachycardia, ventricular fibrillation, flutter, torsade de pointes, or sudden deaths).	

APPEARS THIS WAY ON ORIGINAL



IND126396

**MEETING MINUTES**

Mitsubishi Tanabe Pharma Development America, Inc.  
Attention: Douglas N. Dobak  
Vice President, Regulatory Affairs and Quality Assurance  
525 Washington Blvd., Suite 400  
Jersey City, NJ 07310

Dear Mr. Dobak:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for MCI-186 (edaravone IV bags) for Amyotrophic Lateral Sclerosis.

We also refer to the meeting between representatives of your firm and the FDA on Thursday, 22 October 2015. The purpose of the meeting was to discuss Chemistry Manufacturing and Controls.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me/ Dahlia A. Woody, Regulatory Business Process Manager at (301) 796-8427

Sincerely,

*{See appended electronic signature page}*

Wendy I. Wilson-Lee, Ph.D.  
Branch Chief, Branch I (Acting)  
Division of New Drug Products I  
Office of Pharmaceutical Quality  
Center for Drug Evaluation and Research

Enclosure:  
Meeting Minutes



FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

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**MEMORANDUM OF MEETING MINUTES**

**Meeting Type:** Type B  
**Meeting Category:** Pre-NDA

**Meeting Date and Time:** 10/22/2015  
**Meeting Location:** White Oak, Building 22 Rm 1417

**Application Number:** IND 126396  
**Product Name:** MCI-186  
**Indication:** **Amyotrophic Lateral Sclerosis (ALS)**  
**Sponsor/Applicant Name:** Mitsubishi Tanabe Pharma Development America, Inc.

**Meeting Chair:** Wendy I. Wilson-Lee, Ph.D., Branch Chief (Acting)  
**Meeting Recorder:** Dahlia A. Woody, M.S. PMP

**FDA ATTENDEES**

Wendy I. Wilson-Lee, Ph.D. Branch Chief (Acting)  
Martha R. Heimann, Ph.D. CMC Lead Neurology  
Aditi Thakur, Ph.D.

**SPONSOR ATTENDEES**

Douglas N. Dobak, Vice President, Regulatory Affairs and Quality Assurance, MTDA  
Partha Banerjee, PhD, RAC, Director, CMC, Regulatory, MTDA  
Takayuki Hara, CMC Project Leader, Manager, CMC Strategy and Planning Department, CMC Division, MTPC  
Takeshi Saka, Global Project Leader, Manager, Development Planning and Coordination Department, Development Division, MTPC

**1.0 BACKGROUND**

- (i) The purpose of the meeting is to provide FDA a complete understanding about MCI-186's CMC development history and to obtain the Division's guidance and concurrence on the related questions that must be discussed with the Division before submitting the NDA.
- (ii) MCI-186 (b) (4) (edaravone IV bags) for Amyotrophic Lateral Sclerosis (ALS)

## 2. DISCUSSION

**Question 1:** The proposed specification for the drug substance to be included in the NDA include description, identification, pH, melting point, heavy metals, related substances, loss on drying, residue on ignition and assay which are already listed in JP.

Does the agency agree with the proposed specification for drug substance?

**FDA's Response:**

No. Limits for (b) (4) residual solvents, bioburden (microbial limits) and endotoxins should be included in the drug substance specification. In addition, the impurity specification should include specified, any other individual impurity, and total impurities per ICH Q3A. For (b) (4) consider the options outlined in ICH M7 for control of genotoxic impurities and provide justification for the option chosen. Heavy metals testing should comply with USP (see <231>, <232>, and <233>). Also, please consider the recommendations in the draft ICH Q3D guidance.

**Meeting Discussion:**

There was no discussion at the meeting.

**Question 2:** The starting materials, (b) (4) are commercially available chemicals used for non-pharmaceutical market. Based on the evidence presented, the sponsor considers (b) (4) as appropriate starting materials for synthesis of the drug substance.

Does the agency agree with the proposed starting materials and their specifications and test methods?

**FDA's Response:** (b) (4) are acceptable as regulatory starting materials. However, include limits for impurities in the (b) (4) specification.

**Meeting Discussion:**

There was no discussion at the meeting.

**Question 3a:** The sponsor proposes (b) (4)

(b) (4)

Does the agency agree with this approach?

**FDA's Response:** The Agency does not agree with the proposal (b) (4) for commercial drug product launch. All facilities have to be capable of manufacturing and ready for inspection at the time of application submission. The Agency cannot approve an application referencing a facility (b) (4) that, at the time of application, is not capable of manufacturing the subject drug substance, even if supportive data for previously produced material is available for review. Please be advised that distributing a finished drug product containing a drug substance manufactured in a facility that was not listed in the approved application makes the drug product an unapproved new drug in violation of section 505 of the Federal Food, Drug, and Cosmetic Act.

Finally, any proposed manufacturers in the application must demonstrate compliance to current good manufacturing practices (CGMPs). Typically, a move to a different manufacturing site involves changes, including, but not limited to, the pharmaceutical quality system, manufacturing process, equipment, and personnel. The firm should conduct all studies necessary to qualify the new facility to ensure that it is capable of consistently providing material meeting the required specifications. Please refer to ICH Q7: Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients for further guidance.

ICH Q7: <http://www.fda.gov/downloads/Drugs/.../Guidances/ucm073497.pdf>

**Meeting Discussion:**

There was no discussion at the meeting.

**Question 3b:** Drug product prepared using API from Kashima site (please refer to question 3) has been validated with 3 years of stability at long term condition. We have 6 months of accelerated stability on one batch of drug product using API from Onoda site. Further batches of drug product using API from Onoda site will be manufactured in near future and corresponding long term stability data will be available in future. (b) (4)

Based on the three year stability data at the (b) (4) site for the drug product, the sponsor proposes 3 years shelf life for commercial drug product.

**FDA's Response:** (b) (4)

See the FDA Response to Question #3(a).

**Meeting Discussion:** Although the (b) (4) drug substance manufacturing site is no longer operational, the FDA agreed that, pending review of the data, stability data obtained from drug product manufactured with drug substance from the (b) (4) site may be used to establish the expiration dating period for the commercial product.

The FDA prefers that three months of stability data from drug product batches manufactured with drug substance from the intended commercial drug substance site (Onodo) be included in the submission. However, the Agency is open to further discussion. The Agency may also request additional stability data during the review cycle.

The sponsor indicated that 24 months of stability data are available for drug substance manufactured at the Onodo site.

**Question 4a:** All the excipients are JP grade except phosphoric acid which is Japanese Pharmaceutical Excipients (JPE) grade. This product is stable and is marketed in Japan since 2010. The sponsor proposes to continue to use the same grade excipients for US submission.

Does the agency concur with this approach?

**FDA's Response:** In principle, this approach is reasonable. However, you will need to provide information to support comparability to corresponding USP or NF standards, as appropriate. Additionally, provide copies of the JP and JPE monographs and test methods in the submission.

**Meeting Discussion:**

There was no discussion at the meeting.

**Question 4b:** Sodium bisulfite used as (b) (4) in this product has been used in many other products in Europe and US and is listed as inactive ingredient in higher concentration for injectable products. The sponsor considers sodium bisulfite to be an acceptable excipient for registration of this product in US.

Does the agency concur?

**FDA's Response:** Sodium bisulfite is an acceptable excipient at the proposed level. We remind you that the product labeling should include the warning statement required under 21 CFR § 201.22(b).

**Meeting Discussion:**

There was no discussion at the meeting.

**Question 5:** The IV bag formulation was developed to eliminate the dilution process based on the (b) (4) formulation. In this NDA, the sponsor plans to describe the history of formulation development of edaravone (b) (4) basic idea of formulation development of IV bag (30mg/100mL) based on the (b) (4) supporting stability data of IV bag in formulation development section (P.2. in CTD). The sponsor believes that this information is adequate for describing formulation development.

Does the agency agree?

**FDA's Response:** We agree with this approach.

**Meeting Discussion**

There was no discussion at the meeting.



**Question 7:** The proposed specification for the drug product to be included in the NDA include description, identification, osmolar ratio, pH, related substances, endotoxin, extractable volume, foreign particulate matter, insoluble particulate matter, sterility, and assay.

Does the agency agree with the proposed specification for the drug product?

**FDA's Response:** In general, the proposed test parameters appear appropriate; however, the acceptability of the analytical procedures and acceptance criteria will be a matter for review. At this time, we note the following concerns that should be addressed in the application:

- We recommend that all analytical procedures for the finished product comply with the appropriate USP requirements.
- We recommend that you test the product for osmolality, rather than osmolar ratio, as osmolality is the parameter normally described in labeling for parenteral products.
- The test parameters   <sup>(b) (4)</sup> are unclear. Ensure that the product complies with USP <788> Particulate Matter in Injections and <790> Visible Particulates in Injections.

- The NDA should include data from method suitability testing for the endotoxins and sterility testing methods based on the applicable USP standards.

**Meeting Discussion:**

There was no discussion at the meeting.

**Question 8:** The sponsor has initiated a leachable study using the IV Bags and will have up to 6 months accelerated and room temperature data at the estimated NDA filing time period. The sponsor is committed to submitting ongoing results of this study during the review of the NDA.

Does the agency agree?

**FDA's Response:** As edaravone is not approved in the US, we anticipate that your NDA will be subject to "the Program" under PDUFA V. Therefore, the application is expected to be complete at time of submission. Whether additional information received subsequently will be reviewed during the same review cycle will depend on available Agency resources at the time of submission.

**Meeting Discussion:** Mitsubishi will submit the available data from the formal study in the NDA. Additional data from retained samples stored for three years will also be provided in the submission. The FDA may request any available additional data during the review cycle.

**Question 9:** The sponsor respectfully acknowledges and appreciates FDA's advice on (b) (4) levels per ICH M7. (b) (4)

(b) (4) The sponsor wishes to discuss with FDA setting the specification limits for (b) (4) in the drug substance and drug product based on the testing criteria used. The rationale, our approach to minimize the risks and proposed specifications will be provided in the briefing book package.

Does the agency agree with this proposal?

**FDA's Response:** The acceptability of the proposed limits for (b) (4) will be determined during the review in consultation with the nonclinical team. It is our understanding that you intend to present your rationale for the proposed limits in a future pre-NDA meeting with the entire team. However, given the safety concern, the Agency requests that you include an assessment of whether other approaches (b) (4)

are feasible.

**Meeting Discussion:** The FDA will rely on input from the non-clinical team on the acceptable limit for (b) (4). The sponsor will include information (b) (4) in the drug product in the pharmaceutical development section.

**Question 10:** The sponsor believes that IV bag product and its components; oxygen absorber and oxygen detector [REDACTED] (b) (4) since this is an injectable product although occasional home use may be required.

Does the agency concur?

**FDA's Response:** Requirements for special packaging [REDACTED] (b) (4) are established by the US Consumer Product Safety Commission (CPSC), not FDA. At this time, we are not aware of any requirement for use of special packaging for the IV bag and its components, or any plans to require such packaging.

**Meeting Discussion:**  
There was no discussion at the meeting.

**Question 11:** Regarding environmental assessment, the sponsor considers that no environmental assessment is required and intends to submit a claim for categorical exclusion. Therefore, the sponsor will not adhere to the format specified in the guidance.

Does the agency agree with this approach?

**FDA's Response:** Yes, we concur that you may submit a claim for an environmental categorical exclusion, and it is reasonable to expect that it will be granted. We note that the EIC calculation provided in the briefing package is based on estimated production for use both within and outside the USA. When you submit the NDA, you only need to include the estimated production for use within the USA.

**Meeting Discussion:**  
There was no discussion at the meeting.

**Additional Comments:**  
We remind you to apply for a USAN name.

**Additional Meeting Discussion:**  
The Agency agreed that it is acceptable to use the current compendial Heavy Metals test (per USP <231>) until a new method consistent with USP <232> and <233> is developed and validated.

## 6.0 ATTACHMENTS AND HANDOUTS

1. Background of Stability Batches [REDACTED] (b) (4)

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

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WENDY I WILSON-LEE

11/02/2015



PIND 126396

**MEETING MINUTES**

Mitsubishi Tanabe Pharma Development America, Inc.  
Attention: Douglas N. Dobak,  
Vice President, Regulatory Affairs and Quality Assurance  
525 Washington Blvd, Suite 400  
Jersey City, New Jersey 07310

Dear Mr. Dobak:

Please refer to your Pre-Investigational New Drug Application (PIND) file for edaravone (MCI-186).

We also refer to the meeting between representatives of your firm and the FDA on June 16, 2015. The purpose of the meeting was to the efficacy findings of your Phase 3 study of edaravone for the treatment of ALS and to obtain agreement as to the regulatory pathway needed for approval.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Susan Daugherty, Regulatory Health Project Manager, at (301) 796-0878.

Sincerely,

*{See appended electronic signature page}*

Billy Dunn, MD  
Director  
Division of Neurology Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

Enclosure:  
Meeting Minutes

## MEMORANDUM OF MEETING MINUTES

**Meeting Type:** B  
**Meeting Category:** pre-IND

**Meeting Date and Time:** June 16, 2015 11:00 am  
**Meeting Location:** 10903 New Hampshire Avenue  
White Oak Building #22, Conference Room: 1311  
Silver Spring, Maryland 20903

**Application Number:** PIND 126396  
**Product Name:** edaravone  
**Indication:** amyotrophic lateral sclerosis (ALS)  
**Sponsor/Applicant Name:** Mitsubishi Tanabe Pharma  
**Meeting Chair:** Billy Dunn, MD  
**Meeting Recorder:** Susan Daugherty

### FDA Attendees

Billy Dunn, MD, Director, Division of Neurology Products (DNP)  
Eric Bastings, MD, Deputy Director, DNP  
Ronald Farkas, MD, PhD, Clinical Team Leader, DNP  
Nicholas Kozauer, MD, Clinical Team Leader, DNP  
Christopher Breder, MD, PhD, Clinical Reviewer, DNP  
Kun Jin, PhD, Biometrics Team Leader, Division of Biostatistics I  
Xiangmin Zhang, PhD, Division of Biostatistics I  
Lois Freed, PhD, Supervisory Pharmacologist, DNP  
David Carbone, PhD, Nonclinical Reviewer, DNP  
Martha Heimann, PhD, CMC Lead  
Angela Men, DO, PhD, Clinical Pharmacology Team Leader, Division of Clinical Pharmacology I  
Bilal AbuAsal, PhD, Clinical Pharmacology Reviewer, Division of Clinical Pharmacology I  
Atul Bhattarm, PhD, Pharmacometrics Reviewer  
Nahleen Lopez, PharmD, Regulatory Health Project Manager  
Susan Daugherty, Regulatory Health Project Manager

### Mitsubishi Tanabe Pharma Attendees

Atsuhiko Kawaguchi, PhD, Group Manager, Clinical Pharmacology  
Takeshi Sakata, Global Project Leader, Manager, Development Planning and Coordination  
Department, Development Division  
Fumihiko Takahashi, Statistics, Assistant Manager, Data Science Department  
Partha Banerjee, PhD, RAC, Director, CMC, Regulatory  
Florence Caputo, PhD, Director, Nonclinical Toxicology, Regulatory  
Koji Takei, Senior Manager, Medical Science, Clinical Research  
Joseph M. Palumbo, MD, Vice President, Clinical Research  
Audra C. Durio Senior Regulatory Affairs Specialist

Douglas N. Dobak, Vice President, Regulatory Affairs and Quality Assurance

## 1.0 BACKGROUND

MCI-186 (edaravone) is a compound with free radical-scavenging effects developed by Mitsubishi Tanabe Pharma Corporation (MTPC), and approved in 2001 in Japan for treatment of acute ischemic stroke. A series of clinical studies was completed in Japan in patients with amyotrophic lateral sclerosis (ALS), and MTPC filed a supplemental new drug application (sNDA) with Japan's Pharmaceuticals and Medical Devices Agency (PMDA) for the treatment of ALS on 29 Oct 2014. Edaravone is believed to have a positive effect on mild-to-moderate ALS. A decision is expected in late June 2015.

A teleconference between MTPC 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.

Edaravone received orphan designation for the treatment of ALS on May 12, 2015.

FDA sent Preliminary Comments to the sponsor on June 15, 2015.

Edaravone was approved for the treatment of ALS in Japan on June 26, 2015.

## 2. DISCUSSION

### Clinical

1. Mitsubishi Tanabe Pharma believes that efficacy data from Study MCI186-19 show a favorable difference in ALSFRS-R at study endpoint, as well as at intermediate and extended time points, documenting a lessening of functional decline (of approximately 33%) in the previously identified patients with ALS receiving edaravone versus patients who did not receive active treatment. Hence, the data indicate a slowing of progression of the symptomatology of disease in patients with ALS demonstrated by a change in the functional rating of the ALSFRS-R. These results confirmed earlier observations in Study MCI186-16. In addition, the 6-month extension in Study MCI186-19 further demonstrated a sustained slowing of functional loss up to 12 months in the "definite or probable/EESP/2y" ALS patient population. Does the Agency agree that a clinically meaningful effect was demonstrated?

### Preliminary FDA Response

**On face, some of your results seem to support your claims, and we believe it would be reasonable for you to submit an NDA. However, our initial impression is that uncertainty remains as to whether, or to what degree, the drug might be effective. Some of our concerns include the number and short duration of trials that may be positive.**

(b) (4)  
apparent lack of evidence  
of efficacy in more advanced patients raises concern that the drug may not be

effective in later disease stages, or that efficacy may decrease as disease progresses, even in patients in whom treatment was started early.

We would not require you to conduct additional efficacy studies prior to approval, but encourage you to study a higher dose because it does not seem that the limit of tolerability has been reached, and higher doses could potentially improve efficacy.

**Meeting Discussion**

*The Division encouraged the sponsor to evaluate higher doses, particularly in patients with more advanced disease. This would not be mandatory at the time of NDA submission but could be supportive of the application in addressing the concerns noted in the preliminary comments.*

2. Mitsubishi Tanabe Pharma has over 1.6 million patient exposures to edaravone in the Japanese ischemic stroke population. The sponsor believes that a safety package that includes safety experience from these patients and ALS clinical trials provide adequate safety evidence for edaravone in an NDA. Does the Agency concur?

**Preliminary FDA Response**

Your database contains 349 subjects on edaravone, with an average exposure of about 4 months, or about 12 cycles. This is likely sufficient to support filing an NDA; however, because safety concerns may be discovered during review of your application, the adequacy of the safety database to support approval remains a matter for review.

The information from the Japanese ischemic stroke population should be included as part of your integrated summary of safety. We recognize that this postmarketing data does not have the same rigor in monitoring and collection as information from clinical trials, but the cases can be informative. You should present this data in an organized summary in the integrated summary of safety section of the NDA, and should provide supporting datasets. The original source records should also be submitted in a manner that is searchable and allows retrieval.

**Meeting Discussion**

*The Division acknowledged the shorter treatment duration and population differences between the stroke and ALS programs. The sponsor should include information from the Japanese ischemic stroke program in the ALS submission. The Division is particularly interested in deaths, serious adverse events, and idiosyncratic adverse events (e.g., hypersensitivity/anaphylactic reactions, hepatic and renal dysfunction). These data should be summarized with links to the supporting materials. Electronic datasets will also facilitate evaluation of this information.*

3. In light of the previous human exposure to edaravone for short term use in ischemic stroke patients, Mitsubishi Tanabe Pharma proposes that a Risk Evaluation and Mitigation Strategy and Medication Guide in the postmarketing setting if safety risks are

jointly identified during the NDA review that require risk minimization strategies beyond the professional labeling to ensure that the benefits of edaravone outweigh its risks to the ALS patients. Does the agency agree?

**Preliminary FDA Response**

**At this time, the Office of New Drugs and the Office of Surveillance and Epidemiology have insufficient information to determine whether a risk evaluation and mitigation strategy (REMS) will be necessary to ensure that the benefits of the drug outweigh the risks, and if it is necessary, what the required elements will be. We will determine the need for a REMS during the review of your application.**

**If you choose to voluntarily submit a REMS in the NDA, please refer to the following Guidance for Industry for the correct format and content for your proposal:**

**<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM184128.pdf>**

*There was no discussion of this preliminary response at the meeting.*

4. Mitsubishi Tanabe Pharma believes the following to be true: Japanese ALS treatment protocols are similar to those used in North America, and PK simulation studies show no ethnic differences (Asian versus Caucasian) based on IV administration. Therefore, Mitsubishi Tanabe Pharma believes that a “bridging” study is not necessary. Does the Agency agree?

**Preliminary FDA Response**

**You should clearly address in the NDA the larger issue of whether safety and efficacy results in Japanese ALS patients can be generalized to US patients, based on the data available. We agree this should include evidence supporting your assertion that clinical practice and treatment guidelines related to ALS are similar. You should also directly compare the clinical course of ALS patients in Japan (for example from your placebo arms) to patients at similar disease stage in published US clinical trials.**

**Regarding PK, the analyses you provided are not adequate to support that there are no meaningful differences in PK of your drug between Japanese and Caucasian patients; additional PK analysis is required. We recommend that you submit the raw PK data sets along with any available PK summary tables comparing dose normalized AUC, C<sub>end</sub> to the IND submission. In addition, a population PK approach can be used to calculate and compare the PK parameters of edaravone using race as a covariate.**

*There was no discussion of this preliminary response at the meeting.*

**General Clinical Pharmacology Comments:**

- You need to evaluate drug-drug interaction (DDI) potential with major transporters and the induction/ inhibition potential of major CYP enzymes. Please refer to the FDA DDI guidance for details:  
<http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm292362.pdf>
- You need to characterize CYP enzymes involved in the metabolism of edaravone.
- You need to evaluate the effect of hepatic and renal impairment on the exposure of edaravone.

**Meeting Discussion**

*The sponsor requested clarification regarding the DDI evaluation. The Division clarified that the sponsor needed to conduct in-vitro DDI studies to evaluate any potential transporter or enzyme-mediated interactions.*

*The sponsor mentioned it was not planning to conduct a dedicated QT study and asked if this would be an issue. The Division clarified that the QT study is unlikely to be a filling issue; however, the Division asked the sponsor to submit the available ECG and QT data from previous clinical studies for review.*

**Regulatory**

1. Given the unmet need and high mortality rates in patients with ALS, Mitsubishi Tanabe Pharma wishes to proceed and schedule a pre-NDA meeting to submit our NDA package for priority review. Is the Agency agreeable to such a plan?

**Preliminary FDA Response**

We are open to a pre-NDA meeting to discuss your proposed application. Please note that the purpose of the pre-NDA meeting is to discuss whether the content of the application is adequate and the format acceptable. The meeting package should contain sufficient information so that a decision may be made as to whether your application can be reviewed.

As noted in the guidance for industry Expedited Programs for Serious Conditions – Drugs and Biologics

(<http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm358301.pdf>), the Agency will make a decision regarding priority or standard review at the time of filing of the NDA.

Further guidance on the Pre-NDA meeting is found under *Additional Comments* below, following your Questions and also in an attachment at the end of this document.

*There was no discussion of this preliminary response at the meeting.*

2. The safety and efficacy of edaravone for the treatment of ALS have been evaluated in Japan. Mitsubishi Tanabe Pharma believes that edaravone qualifies for both “Fast Track” and “Breakthrough” designations for the ALS indication. Does the Agency concur?

**Preliminary FDA Response**

Given that edaravone is being developed to treat ALS, a serious disease, and because preliminary review of your clinical data suggests that edaravone has the potential to address an unmet need, you may consider applying for fast track status.

Breakthrough designation (BTD) requires that you provide preliminary clinical evidence that edaravone demonstrates a substantial improvement on a clinically significant endpoint(s) over available therapies. Importantly, BTD would be based on comparison of edaravone to available therapy, i.e., riluzole. The data that you have submitted suggests that it would be difficult to conclude that the efficacy of edaravone is substantially superior from that of riluzole, and we are skeptical that a more detailed comparison would be productive because of major uncertainty introduced by differences in study population and design.

*There was no discussion of this preliminary response at the meeting.*

3. Mitsubishi Tanabe Pharma prefers to proceed to accelerated approval with postmarketing commitments based on the FDA review of the NDA. Does the Agency agree?

**Preliminary FDA Response**

Your question is not clear to us; specific approval pathways available to FDA are a common area of misunderstanding and should be discussed at the meeting.

**Meeting Discussion**

*The Division explained that it would consider all available regulatory pathways for approval that might be appropriate, including both full approval and accelerated approval, based on the data submitted.*

4. Due to the lack of viable treatments for ALS, does the Agency agree that Study MCI186-19 can be used as the pivotal study for the NDA submission with agreed-upon postmarketing commitments?

**Preliminary FDA Response**

See response to Clinical Question 1 and Regulatory Question 3.

*See meeting discussion under Question 1.*

**Additional Comments, Chemistry, Manufacturing, and Controls (CMC) and Nonclinical**

(b) (4)  
Evidence suggests that (b) (4) is a genotoxic carcinogen; therefore, we recommend that you consider approaches to minimize risks related to this impurity (ICH M7, May 2015).

**Meeting Discussion**

*The sponsor requested clarification of the Division's comment that risks related to the (b) (4) impurity be minimized. The Division stated that the sponsor should follow a strategy consistent with guidance (ICH M7). Published literature suggests that (b) (4) is a genotoxic carcinogen. Therefore, (b) (4) should be reduced to a level that would result in a daily dose of not more than 10 µg/day, unless the sponsor has data identifying a more appropriate threshold.*

**Additional Comments** (guidance in preparing for a pre-NDA meeting)

The edaravone NDA is likely to be considered subject to "the Program" under PDUFA V. Therefore, during at the Pre-NDA meeting you should be prepared to discuss and reach agreement with FDA on the content of a complete application, including preliminary discussions on the need for risk evaluation and mitigation strategies (REMS) or other risk management actions. You and FDA may also reach agreement at the meeting on submission of a limited number of minor application components to be submitted not later than 30 days after the submission of the original application. These submissions must be of a type that would not be expected to materially impact the ability of the review team to begin its review. All major components of the application are expected to be included in the original application and are not subject to agreement for late submission.

Include in the meeting package for your pre-NDA meeting, proposals for 1) the content of a complete application and 2) any minor components to be submitted within 30 days after your original submission. You should also include, as part of your meeting questions, a request for our agreement with your proposals.

Discussions and agreements will be summarized at the conclusion of the pre-NDA meeting and reflected in FDA's meeting minutes. If you decide to cancel this meeting and do not have agreement with FDA on the content of a complete application or late submission of any minor application components, your application is expected to be complete at the time of original submission.

In addition, we remind you that the application is expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities.

Information on PDUFA V and the Program is available at <http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm>.

More specific details regarding the formatting of your submission are found in Attachment 1 at the end of this document.

*There was no discussion of these additional comments at the meeting.*

### **3.0 ADDITIONAL INFORMATION**

#### **PREA REQUIREMENTS**

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable. Because this drug product for this indication has an orphan drug designation, you are exempt from these requirements. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.

#### **DATA STANDARDS FOR STUDIES**

CDER strongly encourages IND sponsors to consider the implementation and use of data standards for the submission of applications for investigational new drugs and product registration. Such implementation should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. CDER has produced a web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers. The web page may be found at:

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm>

#### **LABORATORY TEST UNITS FOR CLINICAL TRIALS**

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see [CDER/CBER Position on Use of SI Units for Lab Tests](http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/ucm372553.htm) (<http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/ucm372553.htm>).

#### **ABUSE POTENTIAL ASSESSMENT**

Drugs that affect the central nervous system, are chemically or pharmacologically similar to other drugs with known abuse potential, or produce psychoactive effects such as mood or cognitive changes (e.g., euphoria, hallucinations) need to be evaluated for their abuse potential and a proposal for scheduling will be required at the time of the NDA submission [21 CFR 314.50(d)(5)(vii)]. For information on the abuse potential evaluation and information required at the time of your NDA submission, see the draft guidance for industry, "Guidance for

Industry Assessment of Abuse Potential of Drugs”, available at:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf>.

**4.0 ISSUES REQUIRING FURTHER DISCUSSION**

None

**5.0 ACTION ITEMS**

None

**6.0 ATTACHMENTS AND HANDOUTS**

None

## Attachment 1

### General Clinical Comments related to the pre-NDA Meeting and NDA Submission

The NDA will be reviewed utilizing the CDER Clinical Review Template. Details of the template may be found in the manual of policies and procedures (MAPP) 6010.3 at: <http://www.fda.gov/cder/mapp/6010.3.pdf>.

To facilitate the review, we request you provide analyses, where applicable, that will address the items in the template, including:

1. Section 2.6 Other Relevant Background Information - important regulatory actions in other countries or important information contained in foreign labeling.
2. Section 5.3 Exposure-Response Relationships - important exposure-response assessments.
3. Section 7.1.6 - Less common adverse events (between 0.1% and 1%).
4. Section 7.1.7.3.1 - Laboratory Analyses focused on measures of central tendency. Also provide the normal ranges for the laboratory values.
5. Section 7.1.7.3.2 - Laboratory Analyses focused on outliers or shifts from normal to abnormal. Also provide the criteria used to identify outliers.
6. Section 7.1.7.3.3 - Marked outliers and dropouts for laboratory abnormalities.
7. Section 7.1.8.3.1 - Analysis of vital signs focused on measures of central tendencies.
8. Section 7.1.8.3.2 - Analysis of vital signs focused on outliers or shifts from normal to abnormal.
9. Section 7.1.8.3.3 - Marked outliers for vital signs and dropouts for vital sign abnormalities.
10. Section 7.1.9.1 – Overview of ECG testing in the development program, including a brief review of the nonclinical results.
11. Section 7.1.9.3. – Standard analyses and explorations of ECG data.
12. Section 7.1.16 – Overdose experience.
13. Section 7.4.2.1 - Explorations for dose dependency for adverse findings.
14. Section 7.4.2.2 - Explorations for time dependency for adverse findings.
15. Section 7.4.2.3 - Explorations for drug-demographic interactions.
16. Section 7.4.2.4 - Explorations for drug-disease interactions.
17. Section 7.4.2.5 - Explorations for drug-drug interactions.
18. Section 8.2 - Dosing considerations for important drug-drug interactions.
19. Section 8.3 - Special dosing considerations for patients with renal insufficiency, patients with hepatic insufficiency, pregnant patients, and patients who are nursing.

### Sites for Inspection

To assist the clinical reviewer in selecting sites for inspection, include a table in the original NDA for each of the completed Phase 3 clinical trials that has the following columns:

1. Site number
2. Principle investigator
3. Location: City State, Country
4. Number of subjects screened
5. Number of subjects randomized
6. Number of subjects treated who prematurely discontinued (or other characteristic of interest that might be helpful in choosing sites)
7. Number of protocol violations (Major, minor, definition)

### Common PLR Labeling Deficiencies

#### Highlights:

1. Type size for all labeling information, headings, and subheadings must be a minimum of 8 points, except for trade labeling. This also applies to Contents and the FPI. [See 21 CFR 201.57(d)(6) and Implementation Guidance]
2. The Highlights must be limited in length to one-half page, in 8 point type, two-column format. [See 21 CFR 201.57(d)(8)]
3. The highlights limitation statement must read as follows: 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]. [See 21 CFR 201.57(a)(1)]
4. The drug name must be followed by the drug's dosage form, route of administration, and controlled substance symbol. [See 21 CFR 201.57(a)(2)]
5. The boxed warning is not to exceed a length of 20 lines, requires a heading, must be contained within a box and bolded, and must have the verbatim statement "See full prescribing information for complete boxed warning." Refer to <http://www.fda.gov/cder/regulatory/physLabel/default.htm> for fictitious examples of labeling in the new format (e.g., Imdicon and Fantom) and 21 CFR 201.57(a)(4).

6. For recent major changes, the corresponding new or modified text in the Full Prescribing Information (FPI) must be marked with a vertical line (“margin mark”) on the left edge. [See 21 CFR 201.57(d)(9) and Implementation Guidance].
  7. The new rule [21 CFR 201.57(a)(6)] requires that if a product is a member of an established pharmacologic class, the following statement must appear under the Indications and Usage heading in the Highlights:

“(Drug/Biologic Product) is a (name of class) indicated for (indication(s)).”
  8. Propose an established pharmacologic class that is scientifically valid AND clinically meaningful to practitioners or a rationale for why pharmacologic class should be omitted from the Highlights.
  9. Refer to 21 CFR 201.57 (a)(11) regarding what information to include under the Adverse Reactions heading in Highlights. Remember to list the criteria used to determine inclusion (e.g., incidence rate).
  10. A general customer service email address or a general link to a company website cannot be used to meet the requirement to have adverse reactions reporting contact information in Highlights. It would not provide a structured format for reporting. [See 21 CFR 201.57 (a)(11)]
  11. Do not include the pregnancy category (e.g., A, B, C, D, X) in Highlights. [See comment #34 Preamble]
  12. The Patient Counseling Information statement must appear in Highlights and must read See 17 for PATIENT COUNSELING INFORMATION. [See 21 CFR 201.57(a)(14)]
  13. A revision date (i.e., Revised: month/year) must appear at the end of Highlights. [See 21 CFR 201.57(a)(15)]. For a new NDA, BLA, or supplement, the revision date should be left blank at the time of submission and will be edited to the month/year of application or supplement approval.
  14. A horizontal line must separate the Highlights, Contents, and FPI. [See 21 CFR 201.57(d)(2)]
- Contents (Table of Contents):**
15. The headings and subheadings used in the Contents must match the headings and subheadings used in the FPI. [See 21 CFR 201.57(b)]

16. The Contents section headings must be in bold type. The Contents subsection headings must be indented and not bolded. [See 21 CFR 201.57(d)(10)]
17. Create subsection headings that identify the content. Avoid using the word General, Other, or Miscellaneous for a subsection heading.
18. Only section and subsection headings should appear in Contents. Headings within a subsection must not be included in the Contents.
19. When a subsection is omitted, the numbering does not change.
20. [See 21 CFR 201.56(d)(1)] For example, under Use in Specific Populations, subsection 8.2 (Labor and Delivery) is omitted. It must read as follows:
  - 8.1 Pregnancy
  - 8.3 Nursing Mothers (not 8.2)
  - 8.4 Pediatric Use (not 8.3)
  - 8.5 Geriatric Use (not 8.4)
21. When a section or subsection is omitted from the FPI, the section or subsection must also be omitted from the Contents. The heading “Full Prescribing Information: Contents” must be followed by an asterisk and the following statement must appear at the end of the Contents:

“\*Sections or subsections omitted from the Full Prescribing Information are not listed.”

**Full Prescribing Information (FPI):**

22. Only section and subsection headings should be numbered. Do not number headings within a subsection (e.g., 12.2.1 Central Nervous System). Use headings without numbering (e.g., Central Nervous System).
23. Other than the required bolding [See 21 CFR 201.57(d)(1), (d)(5), and (d)(10)], use bold print sparingly. Use another method for emphasis such as italics or underline. Refer to <http://www.fda.gov/cder/regulatory/physLabel/default.htm> for fictitious examples of labeling in the new format.
24. Do not refer to adverse reactions as “adverse events.” Refer to the “Guidance for Industry: Adverse Reactions Sections of Labeling for Human Prescription Drug and Biological Products – Content and Format,” available at <http://www.fda.gov/cder/guidance>.
25. The preferred presentation of cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. For example, [*see Use in Specific Populations (8.4)*] not *See Pediatric Use (8.4)*. The cross-reference

should be in brackets. Because cross-references are embedded in the text in the FPI, the use of italics to achieve emphasis is encouraged. Do not use all capital letters or bold print. [See Implementation Guidance]

26. Include only references that are important to the prescriber. [See 21 CFR 201.57(c)(16)]
27. Patient Counseling Information must follow after How Supplied/Storage and Handling section. [See 21 CFR 201.56(d)(1)] This section must not be written for the patient but rather for the prescriber so that important information is conveyed to the patient to use the drug safely and effectively. [See 21 CFR 201.57 (c)(18)]
28. The Patient Counseling Information section must reference any FDA-approved patient labeling or Medication Guide. [See 21 CFR 201.57(c)(18)] The reference [See FDA- Approved Patient Labeling] or [See Medication Guide] should appear at the beginning of the Patient Counseling Information section to give it more prominence.
29. There is no requirement that the Patient Package Insert (PPI) or Medication Guide (MG) be a subsection under the Patient Counseling Information section. If the PPI or MG is reprinted at the end of the labeling, include it as a subsection. However, if the PPI or MG is attached (but intended to be detached) or is a separate document, it does not have to be a subsection, as long as the PPI or MG is referenced in the Patient Counseling Information section.
30. The manufacturer information (See 21 CFR 201.1 for drugs and 21 CFR 610 – Subpart G for biologics) should be located after the Patient Counseling Information section, at the end of the labeling.
31. Company website addresses are not permitted in labeling (except for a web address that is solely dedicated to reporting adverse reactions). Delete company website addresses from package insert labeling. The same applies to PPI and MG.
32. If the “Rx only” statement appears at the end of the labeling, delete it. This statement is not required for package insert labeling, only container labels and carton labeling. [See Guidance for Industry: Implementation of Section 126 of the Food and Drug Administration Modernization Act of 1997 – Elimination of Certain Labeling Requirements]. The same applies to PPI and MG.
33. Refer to <http://www.fda.gov/cder/regulatory/physLabel/default.htm> for fictitious examples of labeling in the new format.
34. Refer to the Institute of Safe Medication Practices’ website (<http://www.ismp.org/Tools/abbreviationslist.pdf>) for a list of error-prone abbreviations, symbols, and dose designations.

## **CDISC Data Requests to Sponsors Quantitative Safety and Pharmacoepidemiology Group**

### **Safety Analysis Plan**

In conjunction with the Statistical Analysis Plan which generally addresses statistical issues for efficacy, include a Quantitative Safety Analysis Plan (QSAP). The QSAP should state the adverse events of special interest (AESI), the data to be collected to characterize AESIs, and quantitative methods for analysis, summary and data presentation. The QSAP provides the framework to ensure that the necessary data to understand the premarketing safety profile are obtained, analyzed and presented appropriately. The Clinical Data Interchange Standards Consortium (CDISC) Submission Data Tabulation Model (SDTM) and Analysis Data Model (ADaM) outline the principles for data submission and analysis ([www.cdisc.org](http://www.cdisc.org)).

At a minimum the Safety Analysis Plan should address the following components:

- a. Study design considerations (See: *FDA Guidance to Industry: Pre-Marketing Risk Assessment*, <http://www.fda.gov/CDER/guidance/6357fnl.pdf>).
- b. Safety endpoints for Adverse Events of Special Interest (AESI)
- c. Definition of Treatment Emergent Adverse Event (TEAE)
- d. Expert adjudication process (Expert Clinical Committee Charter)
- e. Data/Safety Monitoring Committee (DSMC): (Submit charter for FDA review) by
- f. Analytical methods (e.g., data pooling or evidence synthesis): statistical principles and sensitivity analyses considered.
- g. When unanticipated safety issues are identified the Quantitative Safety Analysis Plan may be amended. Amendments should be filed in accordance with FDA regulations.

### **Study Data Tabulation Model (SDTM) Issues**

1. The current published SDTM and SDTM Implementation Guide (SDTMIG) carefully should be followed. Refer to the SDTMIG section on Conformance (3.2.3)
2. Domains
  - a. There are additional domains listed below that are not included in the current SDTMIG. Information on these domains may be obtained at [www.CDISC.org](http://www.CDISC.org) and are expected to be published in the next versions of SDTM and SDTMIG (Version 3.1.2). If applicable, use these domains.
    - (DV) Protocol deviations
    - (DA) Drug Accountability
    - (PC, PP) Pharmacokinetics

- (MB, MS) Microbiology
  - (CF) Clinical Findings
- b. The following domains are not available with SDTM but may be included if modeled following the principles of existing SDTM domains.
- Tumor information
  - Imaging Data
  - Complex Inclusion/Exclusion Criteria

### 3. Variables

- a. All required variables are to be included.
- b. All expected variables must be included in all SDTM datasets.
- c. Variables (expected or permissible) for which no values will be submitted must be explicitly stated and discussed with the review division.
- d. A list of all Permissible variables that will be included and those that will not be included for each domain must be provided for review and discussed with the review division.
- e. A list and description of all variables that will be included in the Supplemental Qualifier dataset must be provided.
- f. Do not include any variables in the SDTM datasets that are not specified in the SDTMIG.

### 4. Specific issues of note:

- a. SDTM formatted datasets must not provide replication of core variables (such as treatment arm) across all datasets.
- b. Only MedDRA preferred term and system organ class variables are allowed in the AE domain. However, the other levels of the MedDRA hierarchy may be placed in the SUPPQUAL dataset or an ADaM dataset.
- c. These issues can be addressed through the request for ADaM datasets

### Analysis Data Model (ADaM) Issues

1. Specify which ADaM datasets you intend to submit.
2. Include a list of all variables (including sponsor defined or derived) that will be included in the ADaM datasets.

3. Discuss the structure of the datasets with the reviewing division and specify in the QSAP.
4. Within each adverse event analysis dataset, include all levels of the MedDRA hierarchy as well as verbatim term.
5. Indicate which core variables will be replicated across the different datasets, if any.
6. SDTM and ADaM datasets must use the unique subject ID (USUBJID). Each unique subject identifier must be retained across the entire submission.

### **General Items**

#### Controlled terminology issues

- a. Use a single version of MedDRA for a submission. Does not have to be most recent version
- b. We recommend that the WHO drug dictionary be used for concomitant medications.
- c. Refer to the CDISC terminology for lab test names.
- d. Issues regarding ranges for laboratory measurements must be addressed.

#### **Integrated Summary of Effectiveness**

Please refer to the Guidance for Industry located at the following web page  
<http://www.fda.gov/cder/guidance/7694dft.pdf>

#### **Dataset Comments**

The Division requests the following for the submitted datasets:

1. Provide an integrated safety (adverse event) dataset for all Phase 2 and 3 trials. If the studies are of different design or duration, discuss with the division which studies are most appropriate for integration.

The integrated safety dataset that must include the following fields/variables:

- a. A unique patient identifier
- b. Study/protocol number
- c. Patient's treatment assignment

- d. Demographic characteristics, including gender, chronological age (not date of birth), and race
  - e. Dosing at time of adverse event
  - f. Dosing prior to event (if different)
  - g. Duration of event (or start and stop dates)
  - h. Days on study drug at time of event
  - i. Outcome of event (e.g. ongoing, resolved, led to discontinuation)
  - j. Flag indicating whether or not the event occurred within 30 days of discontinuation of active treatment (either due to premature study drug discontinuation or protocol-specified end of active treatment due to end of study or crossover to placebo).
  - k. Marker for serious adverse events
  - l. Verbatim term
2. The adverse event dataset must include the following MedDRA variables: lower level term (LLT), preferred term (PT), high level term (HLT), high level group term (HLGT), and system organ class (SOC) variables. This dataset must also include the Verbatim term taken from the case report form.
  3. See the attached mock adverse event data set that provides an example of how the MedDRA variables should appear in the data set. Note that this example only pertains to how the MedDRA variables must appear and does not address other content that is usually contained in the adverse event data set.
  4. In the adverse event data set, provide a variable that gives the numeric MedDRA code for each lower level term.
  5. The preferred approach for dealing with the issue of different MedDRA versions is to have one single version for the entire NDA. If this is not an option, then, at a minimum, it is important that a single version of MedDRA is used for the ISS data and ISS analysis. If the version that is to be used for the ISS is different than versions that were used for individual study data or study reports, it is important to provide a table that lists all events whose preferred term or hierarchy mapping changed when the data was converted from one MedDRA version to another. This will be very helpful for understanding discrepancies that may appear when comparing individual study reports/data with the ISS study report/data.
  6. Provide a detailed description for how verbatim terms were coded to lower level terms according to the ICH MedDRA Term Selection: Points to Consider document. For example, were symptoms coded to syndromes or were individual symptoms coded separately.

7. Perform the following SMQ's on the ISS adverse event data and include the results in your ISS report: 1. Severe cutaneous adverse reactions SMQ and 2. Possible drug related hepatic disorders – comprehensive search SMQ. Also, provide any additional SMQ that may be useful based on your assessment of the safety database. Be sure the version of the SMQ that is used corresponds to the same version of MedDRA used for the ISS adverse event data.
8. The spelling and capitalization of MedDRA terms must match the way the terms are presented in the MedDRA dictionary. For example, do not provide MedDRA terms in all upper case letters.
9. Also, for the concomitant medication dataset, you must use the standard nomenclature and spellings from the WHO Drug dictionary and include the numeric code in addition to the ATC code/decode.
10. For the laboratory data, be sure to provide normal ranges, reference ranges, and units as well as a variable that indicates whether the lab result was from the local lab or central lab. Also, the variable for the laboratory result must be in numeric format.
11. Perform adverse event rate analyses at all levels of MedDRA hierarchy (except for LLT) and also broken down by serious versus non-serious.
12. In every dataset, all dates must be formatted as ISO date format.
13. Across all datasets, the same coding must be used for common variables, e.g. "PBO" for the placebo group. Datasets must not incorporate different designations for the same variable, e.g. "PBO" in one dataset, and "0 mg" or "Placebo," in another datasets. If the coding cannot be reconciled, another column using a common terminology for that variable must be included in the datasets.
14. All datasets must contain the following variables/fields (in the same format and coding):
  - a. Each subject must have one unique ID across the entire NDA
  - b. Study number
  - c. Treatment assignment
  - d. Demographic characteristics (age, race, gender, etc.)
15. A comprehensive listing of patients with potentially clinically significant laboratory or vital sign abnormalities must be provided. Also, a listing must be provided of patients reporting adverse events involving abnormalities of laboratory values or vital signs, either in the "investigations" SOC or in an SOC pertaining to the specific abnormality. For example, all AEs coded as "hyperglycemia" (SOC metabolic) and "low blood glucose" (SOC investigations) should be tabulated. The NDA analyses of the frequency of abnormalities across treatment groups is not sufficient without ready identification of the specific patients with such abnormalities. Analyses of laboratory values must include assessments of changes from baseline to worst value, not simply the last value.

16. Provide CRFs for all patients with serious adverse events, in addition to deaths and discontinuations due to adverse events.
17. For patients listed as discontinued to due “investigator decision,” “sponsor request,” “withdrew consent,” or “other,” the verbatim reason for discontinuation (as written in the CRF) should be reviewed to ensure that patients did not dropout because of drug-related reasons (lack of efficacy or adverse effects). If discrepancies are found between listed and verbatim reasons for dropout, the appropriate reason for discontinuation should be listed and patient disposition should be re-tabulated.
18. With reference to the table on the following page, note that the HLGT and HLT level terms are from the primary MedDRA mapping only. There is no need to provide HLT or HLGT terms for any secondary mappings. This mock table is intended to address content regarding MedDRA, and not necessarily other data.

Unique Subject Identifier (USUBJID)	Sequence Number (AESEQ)	Study Site Identifier (SITEID)	Unique Subject Identifier	Coding Dictionary Information	Reported Term for AE (Verbatim)	Lower Level Term MedDRA Code	Lower Level Term (LLT)	Preferred Term High Level Term (HLT)	High Level Group Term (HLGT)	System Organ Class (SOC)	Secondary System Organ Class 2 (SOC2)	Secondary System Organ Class 3 (SOC3)	Secondary System Organ Class 4 (SOC4)
01-701-1015	1	701	1015	MedDRA version 8.0	redness around application site	10003058	Application site redness	Application site redness	Administration site reactions	General disorders and administration site conditions	Skin and subcutaneous tissue disorders		

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WILLIAM H Dunn  
07/16/2015

**LATE-CYCLE COMMUNICATION**  
**DOCUMENTS**



NDA 209176

**LATE-CYCLE MEETING MINUTES**

Mitsubishi Tanabe Pharma Development America, Inc.  
Attention: Douglas N. Dobak  
US Agent for Mitsubishi Tanabe Pharma Corporation  
Vice President, Head of Regulatory Affairs and Quality Assurance  
525 Washington Blvd, Suite 400  
Jersey City, NJ 07310

Dear Mr. Dobak:

Please refer to your New Drug Application (NDA) dated June 16, 2016, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Radicava (edaravone) injection 30 mg/100 mL.

We also refer to the Late-Cycle Meeting (LCM) between representatives of your firm and the FDA on January 31, 2017.

A copy of the official minutes of the LCM is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Jack Dan, RPh, Regulatory Project Manager at (240) 402-6940.

Sincerely,

*{See appended electronic signature page}*

Nick Kozauer, MD  
Cross Discipline Team Leader  
Division of Neurology Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

Enclosure:  
Late Cycle Meeting Minutes



**FOOD AND DRUG ADMINISTRATION**  
CENTER FOR DRUG EVALUATION AND RESEARCH

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**MEMORANDUM OF LATE-CYCLE MEETING MINUTES**

**Meeting Date and Time:** January 31, 2017 at 1:00 pm  
**Meeting Location:** FDA White Oak Campus, Building 22, Room 4270

**Application Number:** NDA 209176  
**Product Name:** Radicava (edaravone)  
**Applicant Name:** Mitsubishi Tanabe Pharma Corporation

**Meeting Chair:** Nick Kozauer, MD  
**Meeting Recorder:** Jack Dan, RPM

**FDA ATTENDEES**

Ellis Unger, MD, Director, Office of New Drugs/Office of Drug Evaluation I  
Nick Kozauer, MD, Cross Discipline Team Leader, Division of Neurology Products (DNP)  
Christopher Breder, MD, Clinical Reviewer  
Lois Freed, PhD, Supervisory Pharmacologist  
David Carbone, PhD, Nonclinical Reviewer  
Wendy Wilson, PhD, Branch Chief (Acting), Drug Product  
Dan Berger, PhD, Drug Product Reviewer  
Elisa Braver, PhD, Division of Epidemiology I  
Donnella Fitzgerald, PharmD, Reviewer, Division of Risk Management (DRISK)  
Sreedharan Sabarinath, PhD, Clinical Pharmacology Team Leader  
Atul Bhattaram, PhD, Pharmacometrics Reviewer  
Xinning Yang, PhD, Clinical Pharmacology Reviewer  
Charlene Flowers, Office of Surveillance and Epidemiology (OSE) Safety Reviewer  
Elisa Braver, PhD, OSE/Office of Pharmacovigilance and Epidemiology (OPE)/Division of Epidemiology I Reviewer  
Tracy Peters, PharmD, Associate Director of Labeling  
Susan Daugherty, Regulatory Project Manager  
Jack Dan, Regulatory Project Manager

**APPLICANT ATTENDEES**

Doug Dobak, Head of Regulatory Affairs  
Rhea Williams, Developmental Regulatory Affairs  
Audra Durio, Regulatory Affairs submissions  
Heeyoung Park, PM Regulatory Affairs  
Ming Ji, Head of Safety  
Elvia Paraiso, Manager, Safety  
Joseph Palumbo, Head of Medical Science and Translational Medicine  
Koji Takei, Medical Science and Translational Medicine and Clinical Development

**1.0 BACKGROUND**

NDA 209176 was submitted on June 16, 2016 for Radicava (edaravone).

Proposed indication: Treatment of Amyotrophic Lateral Sclerosis (ALS)

PDUFA goal date: June 16, 2017

FDA issued a Background Package in preparation for this meeting on January 27, 2017.

## **2.0 DISCUSSION**

### **1. Postmarketing Requirements/Postmarketing Commitments**

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

#### **Discussion:**

The applicant acknowledged the Division's planned postmarketing requirements.

### **2. Review Plans**

#### **Discussion:**

The Division commented that it plans to send its proposed labeling to the applicant as soon as it is available. The Division further indicated that it tentatively plans to take an action on this NDA prior to the June 16, 2017, PDUFA goal date. However, the Division reiterated that a final decision on the application has not yet been made and that it could not provide any target date as to when any such early action may occur.

### **3. Wrap-up and Action Items**

#### **Discussion:**

The applicant was informed that the Agency is unable to discuss the inspection results for their contract manufacturing organization (CMO). The Agency directed the applicant to work directly with its CMO regarding any facilities issues.

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/s/  
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NICHOLAS A KOZAUER  
02/17/2017



Food and Drug Administration  
Silver Spring MD 20993

NDA 209176

**LATE CYCLE  
MEETING  
BACKGROUND  
PACKAGE**

Mitsubishi Tanabe Pharma Development America, Inc.  
Attention: Douglas N. Dobak  
US Agent for Mitsubishi Tanabe Pharma Corporation  
Vice President, Head of Regulatory Affairs and Quality Assurance  
525 Washington Blvd, Suite 400  
Jersey City, NJ 07310

Dear Mr. Dobak:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Radicava (edaravone) injection 30 mg/100 mL.

We also refer to the Late-Cycle Meeting (LCM) scheduled for January 31, 2017. Attached is our background package, including our agenda, for this meeting.

If you have any questions, call Jack Dan, RPh, Regulatory Project Manager, at (240) 402-6940.

Sincerely,

*{See appended electronic signature page}*

Eric Bastings, MD  
Deputy Director  
Division of Neurology Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

ENCLOSURE:  
Late-Cycle Meeting Background Package

## LATE-CYCLE MEETING BACKGROUND PACKAGE

**Meeting Date and Time:** January 31, 2017 at 1:00 pm  
**Meeting Location:** FDA White Oak Campus, Building 22, Room 1201

**Application Number:** NDA 209176  
**Product Name:** Radicava (edaravone)  
**Indication:** Treatment of Amyotrophic Lateral Sclerosis (ALS)  
**Applicant Name:** Mitsubishi Tanabe Pharma Corporation

### FDA ATTENDEES (tentative)

Ellis Unger, MD, Director, Office of New Drugs/Office of Drug Evaluation I  
Billy Dunn, MD, Director, Division of Neurology Products (DNP)  
Eric Bastings, MD Deputy Director, DNP  
Nick Kozauer, MD, Clinical Team Leader, DNP  
Christopher Breder, MD, Clinical Reviewer  
Lois Freed, PhD, Nonclinical Team Leader  
David Carbone, PhD, Nonclinical Reviewer  
Wendy Wilson, PhD, Branch Chief (Acting), Drug Product  
Dan Berger, PhD, Drug Product Reviewer  
Elisa Braver, PhD, Division of Epidemiology I  
Donnella Fitzgerald, PharmD, Division of Risk Management (DRISK) Reviewer  
Corinne Moody, Science Policy Analyst, Controlled Substance Staff  
Sreedharan Sabarinath, PhD, Clinical Pharmacology Team Leader  
Xinning Yang, PhD, Clinical Pharmacology Reviewer  
Katherine Bonson, PhD, Pharmacologist, Controlled Substance Staff  
Lolita White, PharmD, OSE/DMEPA Team Lead  
Charlene Flowers, OSE Safety Reviewer  
Elisa Braver, PhD, OSE/OPE/Division of Epidemiology I Reviewer  
Lucas Kempf, MD, Medical Officer, Rare Diseases  
Aline Moukhtara, RN, OPDP, Regulatory Review Officer  
Tracy Peters, PharmD, Associate Director of Labeling  
Susan Daugherty, Regulatory Project Manager  
Jack Dan, Regulatory Project Manager

### APPLICANT ATTENDEES

Doug Dobak, Head of Regulatory Affairs  
Rhea Williams, Developmental Regulatory Affairs  
Audra Durio, Regulatory Affairs submissions  
Heeyoung Park, PM Regulatory Affairs  
Ming Ji, Head of Safety  
Elvia Paraiso, Manager, Safety  
Joseph Palumbo, Head of Medical Science and Translational Medicine  
Koji Takei, Medical Science and Translational Medicine and Clinical Development

## **INTRODUCTION**

The purpose of a Late-Cycle Meeting (LCM) is to share information and to discuss any substantive review issues that we have identified to date, Advisory Committee (AC) meeting plans (if scheduled), and our objectives for the remainder of the review. The application has not yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader (CDTL) and therefore, the meeting will not address the final regulatory decision for the application. We are sharing this material to promote a collaborative and successful discussion at the meeting.

During the meeting, we may discuss additional information that may be needed to address the identified issues and whether it would be expected to trigger an extension of the PDUFA goal date if the review team should decide, upon receipt of the information, to review it during the current review cycle. If you submit any new information in response to the issues identified in this background package prior to this LCM or the AC meeting, if an AC is planned, we may not be prepared to discuss that new information at this meeting.

## **BRIEF MEMORANDUM OF SUBSTANTIVE REVIEW ISSUES IDENTIFIED TO DATE**

### **1. Discipline Review Letters**

No Discipline Review letters have been issued to date.

### **2. Substantive Review Issues**

No substantive review issues have been identified to date.

## **ADVISORY COMMITTEE MEETING**

An Advisory Committee meeting is not planned.

## **REMS OR OTHER RISK MANAGEMENT ACTIONS**

No issues related to risk management have been identified to date.

## **LCM AGENDA**

1. Introductory Comments – 5 minutes (Nick Kozauer, MD, CDTL/Jack Dan, RPM/Susan Daugherty, RPM)

Welcome, Introductions, Ground rules, Objectives of the meeting.

2. Discussion of Substantive Review Issues

No Substantive Review Issues.

3. Discussion of Minor Review Issues

No Minor Review Issues.

4. Additional Applicant Data

No Additional Applicant Data.

5. Information Requests

There are no pending information requests at this time.

6. Postmarketing Requirements/Postmarketing Commitments – 10 minutes

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

7. Major labeling issues

No major labeling issues.

8. Review Plans – 5 minutes

The Division plans to continue with the ongoing reviews and begin labeling negotiations once we have completed our draft labeling edits.

9. Wrap-up and Action Items – 5 minutes

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/s/  
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ERIC P BASTINGS  
01/27/2017