CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215446Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 138145

MEETING PRELIMINARY COMMENTS

Mitsubishi Tanabe Pharma America, Inc.
Attention: Mr. Patrick Guinn
Executive Director, Regulatory Affairs and CMC Operations
525 Washington Blvd., Suite 400
Jersey City, NJ 07310

Dear Mr. Guinn:

Please refer to your investigational new drug application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for MT-116 (edaravone) oral suspension for the treatment of amyotrophic lateral sclerosis.

We also refer to your June 22, 2021, correspondence, requesting a meeting to discuss the content and format of the data package for submission of a New Drug Application for MT-1186 oral suspension.

Our preliminary responses to your meeting questions are enclosed.

You should provide an electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

In accordance with 21 CFR 10.65(e) and FDA policy, you may not electronically record the discussion at this meeting. The official record of this meeting will be the FDA-generated minutes.

If you have any questions, contact me at michelle.mathers@fda.hhs.gov or at (240) 402-2645.

Sincerely,

{See appended electronic signature page}

Michelle Mathers
Regulatory Project Manager
Neurology 1 Group
Division of Regulatory Operations for Neuroscience
Office of Regulatory Operations
Center for Drug Evaluation and Research

ENCLOSURE:
Preliminary Meeting Comments

U.S. Food and Drug Administration
Silver Spring, MD 20993
www.fda.gov

U.S. FOOD & DRUG ADMINISTRATION

PRELIMINARY MEETING COMMENTS

Meeting Type: Type B
Meeting Category: Pre-NDA

Meeting Date and Time: September 8, 2021; 2:00-3:00 p.m. EDT
Meeting Location: Teleconference

Application Number: IND 138145

Product Name: MT-116 (edaravone) oral suspension
Indication: Amyotrophic lateral sclerosis
Sponsor Name: Mitsubishi Tanabe Pharma Corporation
Regulatory Pathway: 505(b)(1) of the Federal Food, Drug, and Cosmetic Act

FDA ATTENDEES (tentative)

Office of Neuroscience
Billy Dunn, MD, Director

Division of Neurology 1
Eric Bastings, MD, Director (Acting)
Teresa Buracchio, MD, Deputy Director
Emily Freilich, MD, Clinical Team Leader
John Troiani, MD, Clinical Reviewer

Division of Pharmacology/Toxicology - Neuroscience
Lois Freed, PhD, Director
Dave Carbone, PhD, Nonclinical Reviewer

Office of Clinical Pharmacology, Division of Clinical Pharmacology I
Bilal AbuAsal, PhD, Clinical Pharmacology Team Leader
Ramakrishna Samala, PhD, Clinical Pharmacology Reviewer
Atul Bhattaram, PhD Pharmacometrics Team Leader

Office of Pharmaceutical Quality
Martha Heimann, PhD, CMC Lead for Neurology Products

Division of Regulatory Operations for Neuroscience
Michelle Mathers, MS, MBA, Senior Regulatory Project Manager

SPONSOR ATTENDEES

Patrick Guinn, Vice President and Head, Regulatory Affairs and CMC Operations, MTDA
(b) (4), Consultant, Regulatory Affairs, MTDA
Sherry Zhang, Associate Director, Regulatory Affairs and CMC, MTDA
Art Wamil, Executive Director, Neurology, Medical Science, MTDA
(b) (4), Global Clinical Leader and Nonclinical/Clinical Pharmacology Consultant, MTDA
Laura Bower, Sr. Medical Director, Medical Safety Evaluation, Drug Safety, MTDA
Brian Wildstein, Senior Manager, Regulatory Affairs, MTDA
Hiroaki Egawa, Senior Manager, Project Management, MTDA

Introduction:

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for September 8, 2021, between Mitsubishi Tanabe and the Division of Neurology 1. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. However, if these answers and comments are clear to you and you determine that further discussion is not required, you have the option of cancelling the meeting (contact the regulatory project manager (RPM)). If you choose to cancel the meeting, this document will represent the official record of the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). It is important to remember that some meetings, particularly milestone meetings, can be valuable even if the pre-meeting communications are considered sufficient to answer the questions. Contact the RPM if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, as we may not be prepared to discuss or reach agreement on such changes at the meeting.

1.0 BACKGROUND

Mitsubishi Tanabe Pharma Corporation is requesting a Type B pre-NDA meeting to discuss the content and format of a New Drug Application (NDA) for an oral formulation of MT-116 (edaravone) for the treatment of amyotrophic lateral sclerosis (ALS). The sponsor plans to submit the NDA in November of 2021.

Mitsubishi Tanabe received marketing approval for Radicava, an intravenous formulation of edaravone, on May 5, 2017, for the same indication (NDA 209176) and is developing the oral formulation under IND 138145.

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

2.0 DISCUSSION

2.1. Chemistry, Manufacturing, and Controls

(b) (4)

[redacted]

[1] https://www.fda.gov/media/71722/download

(b) (4)

[redacted]

2.2. Clinical

Question 4: The Sponsor has confirmed the food effect in various dose-timing schedules relative to food intake and with various types of meals according to FDA guidance and feedback received on the Post-Marketing Commitment protocol review received 31 October 2018. The results indicate that oral edaravone should be taken following an overnight fast of 8 hours and patients should not consume a meal until at least 1 hour after dose administration. If it is difficult to secure the fasting interval between a meal and edaravone administration, the required fasting interval can be shortened depending on the type of meal, thereby limiting the inconvenience for patients upon administration. The dosing rationale is provided in Section 5.3.1 of this briefing document.

Does the Division agree with the proposed dosing instructions for food effect?

FDA Response to Question 4:
We acknowledge that you have performed food effect studies in various dose-timing schedules with various types of foods. While the data seems supportive of your proposal, the acceptability of the proposed dosing instruction will be a matter of review.

Question 5: The pharmacokinetic (PK) profile after administrations through a PEG tube has been confirmed in ALS patients and through a nasogastric tube in healthy subjects with comparison to oral administrations (Study MT-1186-J05 and Study MT-1186-Z-101). In Study MT-1186-J05, the plasma and urinary PK profiles of unchanged

edaravone and its sulfate and glucuronide conjugates were obtained from ALS subjects given edaravone via a PEG tube. They were compared to those of ALS subjects and healthy subjects given edaravone orally (MT-1186-J04 and Study MT-1186-J03, respectively). Pharmacokinetic disposition profiles and exposure parameters, maximum plasma concentration (Cmax), and area under the concentration-time curve (AUC) did not differ between ALS patients with or without a PEG tube, nor did they differ from normal healthy subjects. In Study MT-1186-Z-101, subjects were administered edaravone via a nasogastric tube (used as a model of PEG administration) or orally, and PK profiles were compared for the same subjects. PK profiles of edaravone after nasogastric tube administration were comparable to those after oral administration. Further details of these studies are provided in Sections 5.4.1 and 5.4.2 of this briefing document.

Does the Division agree that the data support administration of edaravone oral suspension via PEG tube?

FDA Response to Question 5:
We acknowledge that you have conducted a cross study comparison of the plasma exposure data (i.e., AUC and Cmax) from three different studies. The acceptability of this cross study comparison to support administration of edaravone suspension via PEG tube will be a matter of review.

Question 6: As discussed at the EOP2 meeting, the Sponsor conducted a bioequivalence study with 105 mg oral suspension and the approved 60 mg/60 min IV dose (Study MT-1186-J03) to establish a bridge to the IV product. As discussed at a pre-IND meeting (March 2018) and EOP2 meeting (17 July 2019), Study MT-1186-A01 was conducted to support the safety of the oral suspension relative to the IV product. The Sponsor believes that the safety of the oral suspension has been established in Study MT-1186-A01. The incidence rate of adverse events in patients receiving the oral suspension was comparable to that seen with IV edaravone. Further, the most common treatment-emergent adverse events (TEAEs), treatment-emergent serious adverse events (TESAEs), and TEAEs leading to death were associated with ALS disease progression. The topline 24-week data from this open-label safety study is provided in Section 5.5.2 of this briefing document.

Does the Division agree with this assessment?

FDA Response to Question 6:
On face, the 24-week data from study A01 appear adequate to support an NDA submission. The adequacy of the data to support the safety of the oral suspension will be a matter of review.

2.3. Safety

Question 7: The Integrated Summary of Safety (ISS) analysis plan is provided in Section 5.6. The analysis plan details the pooling strategy and specific queries to be presented in the ISS including use of specific standardized MedDRA queries (SMQs) and other important analyses intended to support safety.

Does the Agency agree with the overall safety plan?

FDA Response to Question 7:
We do not agree with the proposed pooling of data from the oral and intravenous (IV) edaravone studies due to differences in the study design and study conduct and the limited interpretability of such pooled data. However, you could instead provide cross-comparison tables within the ISS comparing the safety findings of the two formulations.

The safety datasets from the legacy studies of IV edaravone have already been reviewed in the initial NDA submission, and thus you do not need to resubmit the complete datasets in your NDA submission. As above, cross-comparison tables may be used for any comparisons of the formulations.

The datasets from Study A01 need to be submitted with all data as originally coded, and without any re-adjudication or exclusion of any AEs from the datasets. We acknowledge your concerns regarding the coding of AEs as they relate to possible ALS progression, but we would like to review the data as originally collected and coded. Any recoding of AEs may be done as a supplementary analysis and supplemental datasets may be submitted in addition to the main datasets.

2.4. Administrative

Question 8: Long-term, frequent IV infusions are a highly significant burden for patients with a terminal illness, and for the caretakers and healthcare professionals who help prepare and deliver those infusions to them. The Sponsor developed edaravone oral suspension to deliver a formulation that significantly reduces the burden of administration (either directly or via a feeding tube) as compared to IV edaravone to patients with ALS. The rationale is further described in Section 5.7.

Does the Agency agree with the rationale that the oral suspension formulation of edaravone represents a major contribution to patient care?

FDA Response to Question 8:
Eligibility for 7-years of orphan-drug exclusivity for edaravone oral suspension would be a review issue for the Office of Orphan Products Development (OOPD). OOPD will conduct a review and make a determination for orphan-drug exclusivity upon

marketing approval of edaravone oral suspension. OOPD would then email the applicant a correspondence describing the outcome of the review for the determination for orphan-drug exclusivity for the NDA.

Please also note that as stated in the letter dated May 12, 2015 from the OOPD, orphan-drug designation was granted for the active moiety, edaravone, and not the formulation of the drug.

Question 9: The edaravone oral suspension NDA will be submitted in eCTD format in accordance with the electronic format guidance. The nonclinical and clinical studies, clinical pharmacology, safety and datasets plan, along with the draft table of contents to be provided in the NDA are provided in Section 5.8 of this briefing document.

Does the Division agree that the format and data outlined for submission will be adequate to support the NDA submission of edaravone oral suspension for the treatment of ALS?

FDA Response to Question 9:

1. The following sections found in the proposed Table of Contents (in Appendix E of the briefing package) were shown but no subfolders were added.
   - 1.3.1 Applicant Information
   - 1.6 Meetings
   - 1.7 Fast Track
   - 1.14.4 Investigational Drug Labeling

   If you intend to add any files to any section listed above, you must place the file in a specified sub-folder of that section

   Example: 1.6 Meetings – A "meeting request" must be placed in 1.6.1 Meeting request (not in 1.6 Meetings)

2. The following sections found in the proposed Table of Contents (in Appendix E of the briefing package) were shown to be placed in a sub-folder, but should be placed one level higher.
   - Section 2.3.S.1-2.3.S.7 should all be placed under Section 2.3.S
   - Section 2.3.P.1 thru 2.3.P.8 should all be placed under Section 2.3.P
   - Section 3.2.P.2.1 thru 3.2.P.2.6 should all be placed under Section 3.2.P.2
   - Section 3.2.R.1 thru 3.2.R.2 should be placed in Section 3.2.R

3. Also, **3.2 Regional Information** is not the correct section # for Regional Information incorrect. This should be corrected to **3.2.R Regional Information.**

From a technical perspective (and not content related), the FDA agrees with all other sections of the proposed TOC.

Refer to the *Comprehensive Table of Contents Headings and Hierarchy*[2] and the *M4 Organization of the Common Technical Document for Registration of Pharmaceuticals for Human Use Guidance for Industry*[3] for more details on each module/section referred in the FDA Response.

Question 10: The Summary of Clinical Safety will serve as the ISS for this NDA and meets the space limitations for this section. This approach was deemed appropriate based on the size of the drug development program. The statistical analysis plan, appendices, tables and listings will be presented in Module 5.3.5.3 ISS. The Summary of Clinical Efficacy will serve as the ISE and tables and appendices will be provided in Module 5.3.5.3. The rationale is further described in Section 5.9.

a. Does the Division agree with the plan for the position of the ISS and Clinical Summary of Safety Data in the NDA?

b. Does the Division agree with the plan for the Summary of Clinical Efficacy to serve as the ISE?

FDA Response to Question 10a:
Yes, we agree. See also response to Question 7.

FDA Response to Question 10b:
Yes, we agree.

Please also refer to the standard Division of Neurology 1 pre-NDA safety requests in Attachment 1. We note that not all of the listed analyses may be appropriate for your study population; however, you should conduct those analyses that apply.

3.0 ADDITIONAL INFORMATION

PROSPECTIVE ASSESSMENTS OF SUICIDAL IDEATION AND BEHAVIOR IN CLINICAL PROTOCOLS

Treatment-emergent suicidal ideation and behavior have been identified as a concern for a number of drugs and drug classes. For example, meta-analyses of clinical trial data for both antiepileptic drugs and antidepressants have demonstrated that these drugs increase the risk of suicidal ideation and behavior. Spontaneous reports have led

[2] https://www.fda.gov/media/76444/download
[3] https://www.fda.gov/media/71551/download

to similar concerns with other drugs as well, e.g., isotretinoin and other tretinoins, beta blockers, reserpine, smoking cessation drugs, and drugs for weight loss. Because of these concerns, a prospective assessment for suicidal ideation and behavior should be included, when appropriate and feasible, in clinical trials involving all drugs and biological products for neurological indications. These assessments should generally be included in every clinical protocol, at every visit, and in every phase of development, with the exception of single-dose trials in healthy volunteers. These assessments should be conducted whether or not a particular product is known or suspected to be associated with treatment-emergent suicidal ideation and behavior. A sponsor considering the omission of the assessment of suicidal ideation and behavior from a particular clinical protocol should prospectively discuss this omission with the Division of Neurology 1.

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. Please include a statement that confirms this finding, along with a reference to this communication, as part of the pediatric section (1.9 for eCTD submissions) of your application. 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[4] and Pregnancy and Lactation Labeling Final Rule[5] websites, which include:

- 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

[4] https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information
[5] https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule

format of information related to pregnancy, lactation, and females and males of reproductive potential.

- 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.

Pursuant to the PLLR, you should include the following information with your application to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. The application should include a review and summary of the available published literature regarding the drug's use in pregnant and lactating women and the effects of the drug on male and female fertility (include search parameters and a copy of each reference publication), a cumulative review and summary of relevant cases reported in your pharmacovigilance database (from the time of product development to present), a summary of drug utilization rates amongst females of reproductive potential (e.g., aged 15 to 44 years) calculated cumulatively since initial approval, and an interim report of an ongoing pregnancy registry or a final report on a closed pregnancy registry. If you believe the information is not applicable, provide justification. Otherwise, this information should be located in Module 1. Refer to the draft guidance for industry *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format*.

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

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 guidance for industry *Assessment of Abuse Potential of Drugs*.[6]

[6] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

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)				

To facilitate our facility assessment and inspectional process for your marketing application, we refer you to the instructional supplement for filling out Form FDA 356h[7] and the guidance for industry, *Identification of Manufacturing Establishments in*

[7] https://www.fda.gov/media/84223/download

Applications Submitted to CBER and CDER Questions and Answers[8]*.* Submit all related manufacturing and testing facilities in eCTD Module 3, including those proposed for commercial production and those used for product and manufacturing process development.

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the items described in the draft guidance for industry, *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions,* and the associated conformance guide, *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications,* 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 ORA investigators who conduct those inspections. 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.

Please refer to the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications*.[9]

[8] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/identification-manufacturing-establishments-applications-submitted-cber-and-cder-questions-and
[9] https://www.fda.gov/media/85061/download

ATTACHMENT 1

DN1 Pre-BLA and Pre-NDA Meetings
General Clinical Safety Requests

Datasets:

- Each individual subject should be assigned a single unique subject identifier across the entire application (e.g., including open label extensions of the trials). Include the unique subject identifier in the ISS and individual studies' datasets.
- 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.

For additional guidance refer to the FDA webpage on Study Data Standards Resources.

General Submission Contents:

1. 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
2. Provide an assessment of safety as per the FDA Guidance for Industry: Premarketing Risk Assessment
3. 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.
4. 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.
5. 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)
6. 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.
7. Include active hyperlinks from the lists of references to the referenced article.
8. Provide 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.
9. Include information regarding important regulatory actions in other countries and foreign labeling (translated, if applicable).
10. Submit an annotated version of the pre-BLA meeting minutes that include hyperlinks, when applicable, to the analysis and/or documents requested.

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.
3. Provide a summary table of the original AE coding dictionaries that were used in each of the trials.
4. The preparation of the adverse event dataset for the ISS should include MedDRA Preferred Terms from a single version of MedDRA.
5. Ensure that all adverse events are presented, and not only events deemed "drug-related."
6. Provide a table of treatment-emergent adverse events reported in ≥ 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.
7. Provide a table which summarizes the outcomes of all pregnancies. Provide a table which summarizes all known adverse events in subject offspring.

Narratives and Case Report Forms (CRFs):

1. Provide narratives and case report forms for deaths, adverse events leading to drug discontinuation, SAEs, pregnancies, and AEs of special interest. You should be prepared to supply any additional CRFs or narratives with a rapid turnaround upon request. Narratives should be integrated. For subjects who had more than one event requiring a narrative (whether in the same trial or in the core study and an extension) present a single narrative (rather than separate narratives for the various events).
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 narrative and CRF.
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 laboratory 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 a tabular listing of all subjects with all discontinuations, sorted by reason. The table should include columns for study number, treatment group, unique subject ID, primary reason for drug or study discontinuation. For reasons including Lost to follow-up, Other, Physician/investigator decision, Withdrew consent, and Patient decision, provide more specific information regarding the discontinuation. The Division may want to request selected narratives/CRFs from some of these patients, but they do not need to be submitted at the time of the initial NDA/BLA submission.
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):

a) Patient age and gender
b) Adverse event onset and stop dates (presented as relative Study Day number)
c) Signs and symptoms related to the adverse event being discussed
d) An assessment of the relationship of exposure duration to the development of the adverse event
e) Pertinent medical history
f) Concomitant medications with start dates relative to the adverse event
g) Pertinent physical exam findings
h) Any abnormal vital sign measurements
i) Pertinent test results (e.g., lab data, ECG data, procedures, biopsy data, autopsy results)
j) Discussion of the diagnosis as supported by available clinical data
k) For events without a definitive diagnosis, a list of the differential diagnoses
l) Treatment provided
m) Re-challenge results (if performed)
n) 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, and ECG data.
4. When possible, use the latest version of the National Institutes of Health (NIH) Common Terminology Criteria for Adverse Events (CTCAE) for toxicity grades and shift analyses.
5. 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 ≥7% from baseline and increase of ≥7% from baseline
• Temperature: >38.0 °C, <36.0 °C
• Respiratory rate: <12 breaths/min, > 20 breaths/min

6. Summarize the protocols for collecting ECG data. Summarize the frequency of post-treatment QTc >450 ms, >480 ms, and >500 ms.

Other requests:

1. Patient profiles

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:

a) Age
b) Sex
c) Dates of screening, randomization and starting therapy
d) Whether the patient completed or did not complete the study, with dates and reason for withdrawal
e) 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)
f) Prior medications and concomitant medications with dates of start and end
g) Vital signs and laboratories, sorted by date, with reference ranges *
h) Autopsy reports for all deaths. (If an autopsy report is not available, explicitly state this.)
i) Full reports for radiologic studies, ECG, MRI, pathology results, special studies and procedures with dates and reference ranges
j) 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.
k) For patients who had IND safety report(s), include dates when the initial and follow up safety reports were submitted.

Create a PDF file for each patient and a table of contents with links to each assessment for each patient.

2. Please submit for Division comments an example narrative from a patient who had more than one serious adverse event and participated in the controlled and extension studies prior to submitting your NDA.
3. We request that you submit a sample integrated summary of safety datasets (with data definition file) for Division comments prior to submitting the NDA. This

process could help to identify and resolve any potential issues of navigability or interpretability that could impact the review of your application.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

MICHELLE W MATHERS
09/02/2021 04:33:28 PM

IND 138145

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 investigational new drug application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for MT-1186 (edaravone).

We also refer to the meeting between representatives of your firm and the FDA on July 17, 2019. The purpose of the meeting was to discuss the clinical development plan for the oral formulation of MT-116.

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

If you have any questions, contact Michelle Mathers, Regulatory Project Manager at michelle.mathers@fda.hhs.gov or at (240) 402-2645.

Sincerely,

{See appended electronic signature page}

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

Enclosure:

- Meeting Minutes

U.S. FOOD & DRUG ADMINISTRATION

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: End of Phase 2

Meeting Date and Time: July 17, 2019; 3:00-4:00 p.m. EDT
Meeting Location: White Oak Building 22, Conference Room: 1309

Application Number: IND 138145
Product Name: MT-1186 (edaravone) oral formulation

Indication: Amyotrophic lateral sclerosis
Sponsor Name: Mitsubishi Tanabe Pharma Development America, Inc.

FDA ATTENDEES

Eric Bastings, MD, Deputy Director
Teresa Buracchio, MD, Clinical Team Leader
Rainer Paine, MD, PhD, Clinical Reviewer
Michelle Mathers, Regulatory Project Manager

Office of Clinical Pharmacology
Bilal AbuAsal, PhD, Clinical Pharmacology Reviewer

SPONSOR ATTENDEES

Mitsubishi Tanabe Pharma Development America, Inc.
Laura Bower, Sr. Medical Director, Drug Safety
Doug Dobak, Vice President and Head, Regulatory Affairs and CMC Operations
Heeyoung Park, Director, Commercial Regulatory Affairs
(b) (4), Global Clinical Leader and Nonclinical/Clinical Pharmacology consultant
(b) (4), Consultant, Regulatory Affairs
Sherry Zhang, Senior Manager, Regulatory Affairs

Mitsubishi Tanabe Pharma Corporation
Koji Takei, Global Project Leader, Vice President, Radicava Management Office

1.0 BACKGROUND

Mitsubishi Tanabe Pharma Corporation is requesting a Type B End of Phase 2 meeting to discuss the clinical development plan for an oral formulation of MT-116 (edaravone)

for the treatment of amyotrophic lateral sclerosis (ALS). Mitsubishi Tanabe received marketing approval for Radicava, an intravenous formulation of edaravone, on May 5, 2017, for the same indication (NDA 209176) and is developing the oral formulation under IND 138145.

FDA sent Preliminary Comments to Mitsubishi Tanabe on July 15, 2019. Responses to those comments were provided to the Division on July 16, 2019.

2.0 DISCUSSION

2.1. Nonclinical

Question 1: The Sponsor has completed a 26-week toxicology study in rats and a 39-week toxicology study in dogs. RADICAVA IV post-marketing commitment carcinogenicity studies using edaravone oral suspensions are ongoing. In addition, in order to justify an initial amount of (b) (4) impurity in the proposed final formulation short term and long-term storage, the Sponsor is conducting 13-week toxicology study in rats with oral edaravone containing the (b) (4) impurity.

a) Does the Division agree that no additional nonclinical study is required for initial NDA submission of oral edaravone?

b) Does the Division agree with the proposed approach to justify (b) (4) as an identified impurity in the final formulation?

FDA Response to Question 1a:
Based on the information provided, the completed and ongoing nonclinical studies appear sufficient to support an NDA submission, provided any impurity issues are resolved.

FDA Response to Question 1b:
Your plan to conduct a 13-week toxicology study to qualify (b) (4) is reasonable.

Meeting Discussion: There was no meeting discussion.

2.2. Clinical

Question 2: Study MT-1186-J03 result has demonstrated a 105 mg oral suspension has an equivalent AUC to approved 60 mg/60 min IV dose (geometric mean ratio [90% confidence interval, CI]: 0.977 [0.917, 1.041]). Geometric mean of Cmax of 105 mg oral suspension compared to 60 mg/60 min IV was also within bioequivalence range, but the upper limit of 90% CI exceeded 1.25 (geometric mean ratio [90% CI]: 1.217 [1.090, 1.359]). The plasma levels of these metabolites after

oral administrations were higher than those after IV administrations but are pharmacologically inactive.

Based on results from nonclinical studies in rats and dogs as well as healthy volunteers (Studies MT-1186-J01, -J02, and -J03) using the edaravone oral suspension, there were no significant safety events. A summary of interim results from Study MT-1186-J03 is presented in Appendix 1.

a. Does the Division agree with 105 mg oral suspension can be considered as an equivalent dose compared to 60 mg/60 min IV based on the MT-1186-J03 result and supporting human and nonclinical safety justification?

b. Does the Division agree with the proposed development plan to further confirm safety of 105 mg oral suspension of edaravone?

FDA Response to Question 2a:
Study MT-1186-J03 appears sufficient to establish a bridge to the intravenous (IV) product. Your proposed open-label safety study (MT-1186-A01) will need to support the safety of the increased Cmax and metabolites with the oral suspension, relative to the IV product. Also, see response to Question 3.

FDA Response to Question 2b:
In general, the proposed development plan appears reasonable. Also, see response to Question 3.

Meeting Discussion:
The sponsor stated that it was unclear how the proposed open-label safety study (MT-1186-A01) would fit into the development plan given the Division's responses. The Division replied that study MT-1186-A01 would be a necessary safety study to support the oral edaravone application.

The Division stated that a food effect study would be informative and helpful for labeling. Further details can be discussed at a pre-NDA meeting, but the current food effect study proposal appears adequate.

The sponsor asked if the currently proposed studies would be sufficient for an NDA application. The Division replied that the proposal appears adequate, on face.

The sponsor stated that oral edaravone will probably need to be packaged as a combination product and that a human factors study will be needed based on a CMC meeting with the Agency on April 4. The sponsor asked where this study proposal should be submitted. The Division replied that the request should be sent to the Division and would then be forwarded to the appropriate CMC and human factors/medical errors prevention groups.

Based on discussion that occurred at a Type C meeting held with CMC on April 4, 2019, the sponsor asked if the Division had a mechanism for potentially "fast tracking" their planned NDA application, which would allow the NDA to be accepted with 6 month stability data at the time of submission. The Division replied that this question would need to be discussed with CMC and it would provide a response as a "post-meeting comment" in the meeting minutes.

The sponsor stated that they received the Division's email about the PMC study changes regarding dose escalation. The sponsor is uncertain about the mechanism for releasing the old PMC and issuing a new PMC. The Division replied that PMC study cannot simply be modified, but that a new PMC would need to be issued to reflect the changes in dosing. The sponsor will need to propose new timelines and then a letter releasing the old PMC and issuing a new PMC would be issued.

The sponsor replied that they are far along with planning for the current PMC study and will need to make changes. The Division asked if subjects in the PMC study have already received doses higher than the approved dose, and if there have been any new safety signals. The sponsor replied that there have been no new safety signals and that safety reports have been submitted to the Agency.

Post Meeting Notes:

Clinical
You may submit a request for a Fast Track designation. For further information regarding Fast Track Drug Development Programs, please refer to the FDA document "Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics [1]

Clinical Pharmacology
In the open label safety study, you are administering the suspension after an overnight fasting and up to one hour fasting after drug administration. You should at least wait 2 hours fasting after drug administration before any food intake.

Question 3: The sponsor proposes to conduct a Phase 3 global safety study (MT-1186-A01) administering a105 mg edaravone oral suspension dose for 14 days and 14 days of no-treatment dosing cycles (protocol synopsis included). The sponsor will assess overall safety in ALS patients including potential gastrointestinal (GI) or hepatic adverse events (AEs) associated with the oral administration route.

Based upon the objective, the study is designed and safety data will be obtained from the MT-1186-A01 clinical study.

[1] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/expedited-programs-serious-conditions-drugs-and-biologics

Does the Division agree with the proposed A01 study objective and design to support the NDA?

FDA Response to Question 3:
As your planned NDA would be based on establishing bioequivalence of edaravone oral suspension to the approved IV formulation of edaravone, the proposed safety study (MT-1186-A01) should use the dosing regimen for which efficacy and safety have been established with the approved product. Further, an open-label study design would not be capable of detecting potential differences in efficacy or safety between the two dosing regimens.

Given the prior findings of safety for the approved IV formulation of edaravone, six months of safety data may be adequate to support an NDA submission for edaravone oral suspension and would be consistent with the Guidance for Industry: Determining the Extent of Safety Data Collection Needed in Late Stage Premarket and Postapproval Clinical Investigations[2].

Exploratory efficacy endpoints are not needed for your study and would be difficult to interpret for an open-label safety study.

Meeting Discussion: There was no meeting discussion.

Question 4: Radicava's approved dosing administration for Cycle 1 dosing is 14 days of administration during 14 consecutive days and then 14 days of no-treatment. All subsequent cycles were 10 days of administration during consecutive 14 days and then 14 days of no-treatment. This was established because of the difficulty receiving weekend infusions at clinical sites. Since safety of edaravone within 14-day treatment is established and it is unlikely to cause any safety issue with (b) (4) (b) (4), the sponsor is proposing an oral edaravone dosing regimen of (b) (4) (b) (4) based on additional supporting safety data being generated by A01 study.

Does the Division agree with the proposed approach and dosing regimen for oral edaravone?

FDA Response to Question 4:
See the response to Question 3.

Meeting Discussion:
The sponsor asked why only 6 months of safety data would be needed for study MT-1186-A01 for oral edaravone. The Division replied that 6 months of safety data using

[2] https://www.fda.gov/media/82664/download

the approved dosing regimen would be sufficient because IV edaravone is approved and safety has been established at the planned dosing regimen and exposure levels. The Division noted that a different dosing regimen with more frequent dosing, as currently planned for the PMC study, would require 1 year of safety data to support that regimen for potential inclusion in labeling.

Question 5: The sponsor confirmed significant reductions of Cmax and AUC with food in the initial study MT-1186-J01 and further obtained data regarding the food effect of dosing 1-hour before a high-fat meal and 4-hour after a high-fat meal (Study MT-1186-J02). Since an administration of oral edaravone 4-hour after a high-fat meal could not completely avoid the food effect, the Sponsor has decided that oral edaravone should be administered once daily in the morning on an empty stomach and set this dosing scheme in Study MT-1186-A01. In accordance with the recently issued draft guidance on assessing the effect of food, the sponsor plans to conduct an additional PK study in healthy subjects to investigate the PK profile of oral edaravone relative to different times of administration and different types of meals in detail (Study MT-1186-J06 food effect study). The data from these studies are intended to provide the dosing instruction in the proposed NDA labeling:

a) Does the Division agree with the proposed approach for dosing instruction based on data generated from the planned J06 study?

FDA Response to Question 5:
The proposed approach is acceptable.

Meeting Discussion: There was no meeting discussion.

Question 6: In consideration of high and urgent medical need in this population, the sponsor wishes to file Edaravone Oral Suspension NDA as quickly as possible to deliver this important option to patients and health care professionals, based upon the nonclinical study data, the results from the completed MT-1186-J01 to -J06 studies and 24-week data for 100 patients from the A01 study (MT-1186-A01 will continue up to 48 weeks). With 14-day no-treatment (drug-off) period, no significant safety issue was found with longer duration of treatment for IV Radicava. In order to expedite the NDA submissions of oral edaravone, the sponsor would propose submitting the 24-week safety data in the initial NDA and would commit to submit the 48-week safety data in the 120-day safety update during NDA review.

Does the Division agree this would be an acceptable joint agreement for NDA submission?

FDA Response to Question 6:
See the response to Question 3. All safety data will need to be submitted at the time of NDA submission in order to allow sufficient time for review.

Meeting Discussion: There was no meeting discussion.

2.3. Administrative/Regulatory

Question 7: If the Division requires the A01 for the NDA submission, the sponsor believes that the edaravone oral suspension would qualify for 3-year market exclusivity.

Does the Division agree?

FDA Response to Question 7:
The Agency does not make exclusivity determinations pursuant to sections 505(c)(3)(E) and (j)(5)(F) of the Federal Food, Drug, and Cosmetic Act, and 21 CFR 314.108, until after approval of an NDA. As described at 314.50(j), an applicant should include in its NDA a description of the exclusivity to which the applicant believes it is entitled. FDA will consider the applicant's assertions regarding exclusivity in the review of the application.

Meeting Discussion: There was no meeting discussion.

3.0 ADDITIONAL INFORMATION

Prospective Assessments of Suicidal Ideation and Behavior in Clinical Protocols

Treatment-emergent suicidal ideation and behavior have been identified as a concern for a number of drugs and drug classes. For example, meta-analyses of clinical trial data for both antiepileptic drugs and antidepressants have demonstrated that these drugs increase the risk of suicidal ideation and behavior. Spontaneous reports have led to similar concerns with other drugs as well, e.g., isotretinoin and other tretinoins, beta blockers, reserpine, smoking cessation drugs, and drugs for weight loss. Because of these concerns, a prospective assessment for suicidal ideation and behavior should be included, when appropriate and feasible, in clinical trials involving all drugs and biological products for neurological indications. These assessments should generally be included in every clinical protocol, at every visit, and in every phase of development, with the exception of single-dose trials in healthy volunteers. These assessments should be conducted whether or not a particular product is known or suspected to be associated with treatment-emergent suicidal ideation and behavior. A sponsor considering the omission of the assessment of suicidal ideation and behavior from a

particular clinical protocol should prospectively discuss this omission with the Division of Neurology Products.

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.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End-of-Phase-2 (EOP2) meeting. In the absence of an EOP2 meeting, refer to the draft guidance below. The iPSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The iPSP should be submitted in PDF and Word format. Failure to include an Agreed iPSP with a marketing application could result in a refuse to file action. For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the draft guidance for industry, Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email Pedsdrugs@fda.hhs.gov. For further guidance on pediatric product development, please refer to: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm.

Data Standards for Studies

Under section 745A(a) of the FD&C Act, electronic submissions "shall be submitted in such electronic format as specified by [FDA]." FDA has determined that study data contained in electronic submissions (i.e., NDAs, BLAs, ANDAs and INDs) must be in a format that the Agency can process, review, and archive. Currently, the Agency can process, review, and archive electronic submissions of clinical and nonclinical study data that use the standards specified in the Data Standards Catalog.[3]

[3] http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm

On December 17, 2014, FDA issued the guidance for industry *Providing Electronic Submissions in Electronic Format--- Standardized Study Data.* This guidance describes the submission types, the standardized study data requirements, and when standardized study data will be required. Further, it describes the availability of implementation support in the form of a technical specifications document, Study Data Technical Conformance Guide,[4] as well as email access to the eData Team (cder-edata@fda.hhs.gov) for specific questions related to study data standards. Standardized study data will be required in marketing application submissions for clinical and nonclinical studies that started after December 17, 2016. Standardized study data will be required in commercial IND application submissions for clinical and nonclinical studies that started after December 17, 2017. CDER has produced a Study Data Standards Resources web page[5] 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.

Although the submission of study data in conformance to the standards listed in the FDA Data Standards Catalog will not be required in studies that started on or before December 17, 2016, CDER strongly encourages IND sponsors to use the FDA supported data standards for the submission of IND applications and marketing applications. The implementation of data standards 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. For clinical and nonclinical studies, IND sponsors should include a plan (e.g., in the IND) describing the submission of standardized study data to FDA. This study data standardization plan (see the Conformance Guide) will assist FDA in identifying potential data standardization issues early in the development program.

If you have not previously submitted an eCTD submission or standardized study data, we encourage you to send us samples for validation following the instructions at FDA.gov.[6] For general toxicology, supporting nonclinical toxicokinetic, and carcinogenicity studies, submit data in the Standards for the Exchange of Nonclinical Data (SEND) format. The validation of sample submissions tests conformance to FDA supported electronic submission and data standards; there is no scientific review of content.

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4 http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf

5 http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm

6 https://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/Electro nicSubmissions/ucm174459.htm

The Agency encourages submission of sample data for review before submission of the marketing application. These datasets will be reviewed only for conformance to standards, structure, and format. They will not be reviewed as a part of an application review. These datasets should represent datasets used for the phase 3 trials. The FDA Study Data Technical Conformance Guide[7] (Section 7.2 eCTD Sample Submission pg. 30) includes the link to the instructions for submitting eCTD and sample data to the Agency. The Agency strongly encourages Sponsors to submit standardized sample data using the standards listed in the Data Standards Catalog referenced on the FDA Study Data Standards Resources web site.[8] When submitting sample data sets, clearly identify them as such with **SAMPLE STANDARDIZED DATASETS** on the cover letter of your submission.

Additional information can be found at FDA.gov.[9]

Discussion of Safety Analysis Strategy for the ISS

After initiation of all trials planned for the phase 3 program, you should consider requesting a Type C meeting to gain agreement on the safety analysis strategy for the Integrated Summary of Safety (ISS) and related data requirements. Topics of discussion at this meeting would include pooling strategy (i.e., specific studies to be pooled and analytic methodology intended to manage between-study design differences, if applicable), specific queries including use of specific standardized MedDRA queries (SMQs), and other important analyses intended to support safety. The meeting should be held after you have drafted an analytic plan for the ISS, and prior to programming work for pooled or other safety analyses planned for inclusion in the ISS. This meeting, if held, would precede the Pre-NDA meeting. Note that this meeting is optional; the issues can instead be addressed at the pre-NDA meeting.

To optimize the output of this meeting, submit the following documents for review as part of the briefing package:

- Description of all trials to be included in the ISS. Please provide a tabular listing of clinical trials including appropriate details.

- ISS statistical analysis plan, including proposed pooling strategy, rationale for inclusion or exclusion of trials from the pooled population(s), and planned

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[7] https://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf

[8] https://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm

[9] http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm

analytic strategies to manage differences in trial designs (e.g., in length, randomization ratio imbalances, study populations, etc.).

- For a phase 3 program that includes trial(s) with multiple periods (e.g., double-blind randomized period, long-term extension period, etc.), submit planned criteria for analyses across the program for determination of start / end of trial period (i.e., method of assignment of study events to a specific study period).

- Prioritized list of previously observed and anticipated safety issues to be evaluated, and planned analytic strategy including any SMQs, modifications to specific SMQs, or sponsor-created groupings of Preferred Terms. A rationale supporting any proposed modifications to an SMQ or sponsor-created groupings should be provided.

When requesting this meeting, clearly mark your submission "**DISCUSS SAFETY ANALYSIS STRATEGY FOR THE ISS**" in large font, bolded type at the beginning of the cover letter for the Type C meeting request.

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 the FDA website entitled Study Data Standards Resources[10] and the CDER/CBER Position on Use of SI Units for Lab Tests website.[11]

Submission Format Requirements

The Electronic Common Technical Document (eCTD) is CDER and CBER's standard format for electronic regulatory submissions. The following submission types: **NDA, ANDA, BLA, Master File** (except Type III) and **Commercial INDs** must be submitted in eCTD format. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit FDA.gov.[12]

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[10] http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm

[11] https://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM587505.pdf

[12] http://www.fda.gov/ectd

The FDA Electronic Submissions Gateway (ESG) is the central transmission point for sending information electronically to the FDA and enables the secure submission of regulatory information for review. Submissions less than 10 GB must be submitted via the ESG. For submissions that are greater than 10 GB, refer to the FDA technical specification *Specification for Transmitting Electronic Submissions using eCTD Specifications*. For additional information, see FDA.gov.[13]

Secure Email Communications

Secure email is required for all email communications from FDA when confidential information (e.g., trade secrets, manufacturing, or patient information) is included in the message. To receive email communications from FDA that include confidential information (e.g., information requests, labeling revisions, courtesy copies of letters), you must establish secure email. To establish secure email with FDA, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications (except for 7-day safety reports for INDs not in eCTD format).

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 guidance for industry *Assessment of Abuse Potential of Drugs*.[14]

4.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

5.0 ACTION ITEMS

There were no action items.

6.0 ATTACHMENTS AND HANDOUTS

There were no handouts for this meeting.

[13] http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway

[14] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

ERIC P BASTINGS
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