CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215887Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 124264

MEETING MINUTES

Biogen Inc.
Attention: Priya Singhal, MD, MPH
Vice President, Regulatory Affairs
225 Binney St.
Cambridge, MA 02142

Dear Dr. Singhal:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for tofersen (BIIB067).

We also refer to the telecon between representatives of your firm and the FDA on April 1, 2022. The purpose of the meeting was to discuss the content and format of a New Drug Application for tofersen.

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}

Teresa Buracchio, MD
Director
Division of Neurology 1
Office of Neuroscience
Center for Drug Evaluation and Research

Enclosure:

- Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Pre-NDA

Meeting Date and Time: April 1, 2022; 11:00 a.m.-12:00 p.m. EDT
Meeting Location: Teleconference

Application Number: IND 124264
Product Name: Tofersen (BIIB067)

Indication: SOD1-amyotrophic lateral sclerosis
Sponsor Name: Biogen, Inc.
Regulatory Pathway: 505(b)(1) of the Federal Food, Drug, and Cosmetic Act

FDA ATTENDEES

Office of New Drugs
Peter Stein, MD, Director

Office of Neuroscience
Billy Dunn, MD, Director
Michelle Campbell, PhD, Associate Director for Clinical Outcomes and External Engagement

Division of Neurology 1
Teresa Buracchio, MD, Director
Laura Jawidzik, MD, Deputy Director (Acting)
Emily Freilich, MD, Clinical Team Leader
Rainer Paine, MD, PhD, Clinical Reviewer
Kevin Krudys, PhD, Senior Clinical Analyst
Sally Jo Yasuda, PharmD, MS, Clinical Safety Team Leader
Natalie Branagan, MD, Clinical Safety Reviewer

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

Office of Biostatistics
Kun Jin, PhD, Biometrics Team Leader, Biometrics I
Tristan Massie, PhD, Statistical Reviewer

Office of Clinical Pharmacology
Bilal AbuAsal, PhD, Clinical Pharmacology Team Leader, DNP, OCP
Xiaohan Cai, PhD, Clinical Pharmacology Reviewer, DNP, OCP
Hobart Rogers, PharmD, PhD, Reviewer
Atul Bhattaram, PhD, Pharmacometrics Team Leader

Division of Regulatory Operations for Neuroscience
Michelle Mathers, MS, MBA, Senior Regulatory Project Manager
Terry Harrison, PharmD, Safety Regulatory Project Manager

Controlled Substances Staff
Neil Varshneya, PhD, Pharmacologist

Office of Surveillance and Epidemiology
Lopa Thambi, PharmD, Safety RPM

Division of Medication Error Prevention and Analysis
Chad Morris, PharmD, MPH, Safety Evaluator

Division of Risk Management
Carla Darling, PharmD, BCPS, Risk Management Analyst

SPONSOR ATTENDEES
Barbara Kolb, MBA, Head of US Regulatory Sciences and Global Regulatory Policy
Laura Fanning, MD, Senior Medical Director, Global Medical Safety
Toby Ferguson, MD, PhD, Head of Neuromuscular Development Unit
Stephanie Fradette, PharmD, Senior Medical Director, Clinical Development
Danielle Graham, PhD, Senior Director, Fluid Biomarkers
Manjit McNeill, MSc, Director, Biostatistics
Cecelia Moran, Manager, US Regulatory Sciences
Ivan Nestorov, PhD, Senior Director, Clinical Pharmacology & Pharmacometrics
Michelle O'Brien, Director, Global Regulatory CMC Lead
Mark Rutter, Senior Director, US Regulatory Sciences
Peng Sun, PhD, Senior Director, Biostatistics
Mark Swarz, Director, Global Regulatory Science

1.0 BACKGROUND

Tofersen (BIIB067) is an antisense oligonucleotide (ASO) being developed by Biogen under IND 124264 for the treatment of amyotrophic lateral sclerosis (ALS) in adults who have a confirmed mutation of the superoxide dismutase 1 (SOD1) gene. IND 124264 was submitted to the Agency on October 28, 2015, and was granted fast track designation on December 23, 2015. Orphan designation for the treatment of SOD1-ALS was granted on September 19, 2019.

On January 7, 2022, Biogen requested a Type B meeting to discuss the content and format of an original New Drug Application (NDA) for tofersen. Specifically, the sponsor requested the Agency's feedback on the following items:

- Incorporation of supportive information from a January 2022 data-cut as part of the initial NDA
- Plans for a safety update mid-NDA review to support the assessment of tofersen for registration
- Intended scope of data to be provided for the bioanalytical (BA) methods tables in the NDA
- Implementation of an expiry date format based on updates to United States Pharmacopeia (USP) Chapter 7
- A detailed table of contents (TOC) of the upcoming 505(b)(1) New Drug Application
- Understand the potential viability of an accelerated approval pathway and the utility of plasma NfL as a surrogate endpoint for tofersen

FDA sent Preliminary Comments to Biogen on March 29, 2022.

2.0 DISCUSSION

2.1. Clinical Efficacy/Statistics

Question 1: An interim cut of the ongoing open-label extension Study 233AS102 was performed on 16 January 2022; a clinical interim database lock (DBL) is planned for 28 February 2022. These data are being analyzed to confirm trends on clinical outcomes and survival remain consistent with those observed in the original interim cut from 16 July 2021. This subsequent interim cut offers approximately 6 months of additional follow up.

These analyses are being conducted in accordance with the amended Statistical Analysis Plans submitted to the Agency on 08 February 2022 (Seq. 0180). The Sponsor proposes to include these data and their integration with data from Study 233AS101 as part of the NDA as follows:

- Study 102 16Jan2022 interim data will be summarized in a separate interim clinical study report (CSR). There will be 2 separate eSubmission (eSub) packages for each of the interim cuts, one for the 16July2021 interim cut and one for the 16Jan2022 interim cut. The SDTM and ADaM folders under the Study 102 eSub folder will have separate subfolders for each of these interim cuts.
- Integration of data from Study 101 and the Study 102 16 Jan 2022 interim cut will be summarized in addenda to Module 2.5 Clinical Overview, Module 2.7.3 Summary of Clinical Efficacy and Module 2.7.4 Summary of Clinical Safety. There will be 2 separate eSub packages consisting of integrated ADaM

datasets and programs with corresponding documentation for each of the separate interim cuts of 16 July 2021 and 16 Jan 2022. There will be one eSub folder for each of the safety ADaM and efficacy ADaM, both with separate subfolders for each interim cut.

- As part of the 16Jan2022 interim cut, the Sponsor has implemented vital status checks via the study sites for participants who have completed participation in Studies 101 or 102 (i.e., those who did not continue into Study 102 or those who have withdrawn from either study). These data will be incorporated in a supplementary analysis of overall survival in the overall population (early vs. delayed-start tofersen) and the subset of tofersen-treated A5V carriers (n=16). These data are being collected retrospectively and therefore, will be incorporated in a support file, and will form part of the Reviewers Guide under the efficacy eSub folder for Module 2.7.

Does the Agency agree with the approach as outlined by Biogen?

FDA Response to Question 1:

We have no objection to your proposals to include separate eSub folders for the two interim data cuts or to include supplementary analysis addenda pooled from both the primary and extension studies. Note that the submission will need to include the efficacy and safety data from the individual studies separately.

Meeting Discussion:
This question was not discussed during the meeting.

2.2. Safety Statistics

Question 2: In accordance with 21 CFR 314.50 (d)(5)(vi)(b), the Sponsor is preparing for a safety update to support the 505(b)(1) NDA review. An estimated data cut-off of 15 July 2022 is being proposed as approximately 1-year will have elapsed since the July 2021 NDA data cut and 6 months since the January 2022 interim data cut of Study 233AS102. Safety information to be provided at this time will include data from the ongoing Study 233AS102, AEs and SAEs from the expanded access program launched by the Sponsor, and a blinded aggregate safety summary from Study 233AS303 (presymptomatic; ATLAS).

The Sponsor would request confirmation of the following:

a) ***Does the Agency agree with the proposed safety update data cut-off date of 15 July 2022?***
b) ***Does the Agency agree with the proposal to include cumulative data summaries from Study 233AS102?***

c) Does the Agency agree with the proposal to include safety information related to AEs and SAEs from the expanded access program?

d) Does the Agency agree with the proposal to include cumulative blinded data summaries from Study 233AS303?

FDA Response to Question 2a:

The proposed plan to use a July 15, 2022, cut-off date for the safety update, which would allow for at least 12 months of safety data from all pivotal trial subjects, appears reasonable; however, the acceptability of the July cut-off date will ultimately depend on the date of the initial NDA submission.

Please also refer to the Appendix of General Clinical Safety Requests at the end of this document when preparing for the NDA submission. Note that the General Clinical Safety Requests are common requests for safety analyses that should be considered for inclusion in the safety summary; however, the requests may not be applicable to all study populations. You should include the requests that are appropriate for your study population.

Meeting Discussion:
This question was not discussed during the meeting.

FDA Response to Question 2b:

Yes. See also the response to Question 1.

Meeting Discussion:
This question was not discussed during the meeting.

FDA Response to Question 2c:

Yes. Narratives should also be included for all SAEs from the expanded access program.

Meeting Discussion:
This question was not discussed during the meeting.

FDA Response to Question 2d:

Cumulative blinded data summaries from the ongoing Study 233AS303 are not necessary; however, line listings of the available safety data and blinded reports of all

deaths, SAEs, and discontinuations due to adverse events should be included.

Meeting Discussion:
This question was not discussed during the meeting.

2.3. Clinical Pharmacology/Biopharmaceutics

Question 3: In consideration of FDA's *Guidance to Industry: Bioanalytical Methods Templates*, the Sponsor confirms the intent to provide the requested tables as an appendix to Module 2.7.1 Summary of Biopharmaceutics for the pharmacokinetic assays associated with the program. Tables will not be provided for pharmacodynamic assays.

Does the Agency agree?

FDA Response to Question 3:

No, we do not agree. Please submit the summary tables for the pharmacodynamic assays used to support the biomarker quantitation. In addition, you need to submit the validation and sample analysis reports for the relevant biomarker data used to support the NDA submission.

Meeting Discussion:
This question was not discussed during the meeting.

2.4. Chemistry, Manufacturing and Controls

Question 4: The Sponsor intends to proactively implement the expiration date format of YYYY-MM for the final tofersen commercial label and packaging to align with modifications to United States Pharmacopeia (USP) Chapter 7 anticipated to take effect in 2023. **Does the Agency agree with this approach?**

FDA Response to Question 4:

The acceptability of the expiration date format depends on whether you intend to use numerical or alphabetical characters to represent the month portion of the expiration date. YYYY-MM is acceptable if only numerical characters are used (for example, 2023-06) to represent the month. YYYY-MMM is acceptable if alphabetical characters are used (for example, 2023-JUN) to represent the month.

Meeting Discussion:
This question was not discussed during the meeting.

2.5. Regulatory

Question 5: The Sponsor intends to submit the statistical analysis plans and corresponding datasets associated with the Integrated Summary of Efficacy and Integrated Summary of Safety in Module 5.3.5.3 Reports of Analyses of Data from More than One Study while describing the results within Module 2.7.3 Summary of Clinical Efficacy and Module 2.7.4 Summary of Clinical Safety, respectively.

Does this Agency agree with this approach?

FDA Response to Question 5:

Yes, your proposed approach appears consistent with Section IIIC of the Guidance for Industry: Integrated Summaries of Effectiveness and Safety: Location Within the Common Technical Document.[1]

Meeting Discussion:
This question was not discussed during the meeting.

Question 6: The Sponsor intends to submit a 505(b)(1) New Drug Application later in Q2 2022. A comprehensive Table of Contents (TOC) for the forthcoming NDA will be provided as part of the briefing book, including information on the anticipated Module 1 documentation.

Does the Agency agree that the proposed NDA content is sufficient for registration?

FDA Response to Question 6:

The proposed content looks appropriate to support review of an NDA submission, with the following comments.

- Forms 356h, 3397, and 3674 should be placed in Section 1.1 (Forms). The proposed eCTD Table of Contents for planned NDA submission contains Form 356h, Form 3397, and Form 3674 in Section 1.1.2., 1.1.3, and 1.1.7, respectively. Please refer to the Comprehensive Table of Contents Headings and Hierarchy Section 1.1 Forms for more details.

[1] https://www.fda.gov/media/75783/download

- The other sections provided in the TOC appear acceptable. We note that the following additional information should also be included in the NDA submission:

  - Please provide exposure-response analysis reports to support tofersen's effects on clinical endpoints and pharmacodynamic biomarkers.

  - If available, please provide PK and PD data from ALS patients that underwent autopsy to confirm the PK/PD model used to simulate SOD1 mRNA target engagement in human tissue.

  - Please clarify whether you have evaluated the immunogenicity of tofersen. If yes, please submit the validation and sample analysis reports for immunogenicity assessments, as well as an integrated summary of immunogenicity.

Meeting Discussion:
The sponsor confirmed that the available PK/PD data from ALS patients who underwent autopsy will be included in the future NDA submission.

Question 7: As originally communicated at the Type C meeting on 21 December 2021, our intention remains to submit a NDA for tofersen for the treatment of ALS associated with a mutation in the SOD1 gene. The clinical results demonstrate a biological effect and, acknowledging the study did not achieve the prespecified primary endpoint, the Sponsor would like the Agency's advice at the Pre-NDA meeting on alternative regulatory pathways. Specifically, the Sponsor would like to solicit the Division's feedback on the potential to grant marketing authorization for tofersen via the accelerated approval pathway as described in 21 CFR 314 Subpart H. The primary evidence we would propose would be the change from baseline to Week 28 in plasma neurofilament light chain (NfL) as a surrogate endpoint that is reasonably likely to predict clinical outcomes.

Would the Agency please comment on the potential viability of an accelerated approval pathway and the utility of plasma NfL as a surrogate endpoint?

FDA Response to Question 7:

We are prepared to consider an NDA submission intended to support accelerated approval. This answer should not be construed to suggest that we have prospectively concluded that the effect you have reported on plasma NfL is reasonably likely to predict clinical benefit. Your application should establish both that substantial evidence exists for the effect of tofersen on plasma NfL and that such an effect is reasonably likely to predict clinical benefit. Presumably, such an argument would include (but may not be limited to) a discussion of the other biomarker (CSF SOD-1 protein, CSF NfL, plasma phosphyorylated neurofilament heavy chain (pNF-H), CSF pNF-H) and clinical

outcome data you have obtained.

Meeting Discussion:

The sponsor summarized the results of Study 233AS101 (pivotal study) and 233AS102 Open-Label Extension (OLE), focusing on the observed reductions in NfL and SOD1 protein in the tofersen treatment group compared to placebo, as well as the clinical trends from the comparisons of early-start and placebo/delayed-start tofersen groups. The sponsor confirmed that the presented week 52 data included all subjects, not the prespecified or post hoc subgroup analyses. Although the sponsor continues to find relevance in the post hoc subgroups stratified by baseline NfL level, the sponsor feels that the data demonstrate a separation in benefit regardless of baseline NfL level and intends to provide data on the whole study population in the NDA submission. The sponsor plans to submit all components of the NDA at the time of submission, with no plans to submit a REMS. The sponsor expects to submit an NDA on May 31, 2022, but may delay submission until June if more time is needed.

The Division noted the sponsor's change in approach from the traditional approval pathway presented by the sponsor in the prior meeting to an accelerated approval pathway. The sponsor stated that after internal consideration of the Division's feedback on the Phase 3 study results, it determined that accelerated approval would be the best path forward. The sponsor recognizes this is a complex program with emerging data but is confident in the treatment benefit and hoping to find the most appropriate pathway to move forward.

The Division stated that in order to support accelerated approval, the NDA submission would need to provide substantial evidence of effectiveness on the endpoint intended to support accelerated approval (i.e., change from baseline to Week 28 in plasma NfL, per the sponsor's current proposal) and would need to establish that the effect on that endpoint is reasonably likely to predict clinical benefit. The Division also noted that the sponsor should provide comprehensive analyses of all the available biomarker data, including the correlation between clinical outcomes and the biomarkers over time. The sponsor should address the relationships between cerebrospinal fluid (CSF) and blood measurements of the proposed biomarkers in patients with ALS and in other neurodegenerative conditions. Given the individual variability of biomarkers, the Division also recommended including other metrics such as Area Under the Curve (AUC), when possible. The sponsor should include analytical reports for the biomarkers in the NDA submission.

The sponsor proposed that, should accelerated approval be granted, the datato confirm the benefit of tofersen in ALS would come from either survival data in the OLE, or the ongoing study in presymptomatic patients (Study 303/ATLAS). The Division noted that open-label data from an extension study could have

interpretability concerns. The sponsor indicated that the OLE has protected the blind to original treatment and there is ongoing analytical work on how to operationalize the study data to provide confirmatory evidence of clinical benefit. Study 303 in pre-symptomatic SOD1 mutation carriers currently has 53 patients enrolled in the natural history Part A of the study, and one patient has enrolled in the randomized, double-blind Part B. The sponsor will weigh the advantages and disadvantages of each confirmatory study approach.

Regarding Study 303 in presymptomatic patients, the Division encouraged the sponsor to engage with the Division on potential approaches to conduct a rigorous interim analysis to obtain an early indicator of treatment benefit given the currently long estimated length of study.

The Division inquired about any additional safety data from the recent data cut in the OLE. The sponsor cited some ongoing safety signals, such as myelitis, but stated that there were no new safety signals that emerged from longer exposure. There was a single case of increased intracranial pressure and papilledema that did not lead to study discontinuation.

The Division also asked about the number of patients with the fast-progressing A4V mutation that remained in the study. The sponsor reported three A4v mutation carriers remain in the study with a median survival of 1.74 years and that one patient is ongoing and will surpass the 4-year maximum survival reported in the literature in July 2022. The sponsor stated that these three patients are reported to be doing well.

The sponsor confirmed that the upcoming NDA submission in the United States would be the first regulatory application world-wide for tofersen.

3.0 ADDITIONAL INFORMATION

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application was discussed.

- 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.

- A preliminary discussion was held on the need for a REMS, other risk management actions and, where applicable, the development of a Formal Communication Plan and it was concluded that you do not intend to submit a REMS with 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.

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[2] and Pregnancy and Lactation Labeling Final Rule[3] 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 format of information related to pregnancy, lactation, and females and males of reproductive potential.

- Regulations and related guidance documents.

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

- 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

1. 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 NDA submission [21 CFR 314.50(d)(5)(vii)]. For information on the abuse potential evaluation and information required at the time of NDA submission, see the guidance for industry, Assessment of Abuse Potential of Drugs (https://www.fda.gov/media/116739/download). We recommend that, in a future submission to your IND, you discuss the available abuse potential-related nonclinical and clinical data and, within the framework of the referenced guidance, propose how you intend to assess potential for abuse and physical dependence.

2. Capture abuse-related adverse events (AEs) during clinical studies and provide detailed narratives for these AEs. Provide a list of terms that will prompt these reports (including abuse-related AE terms such as euphoria, dissociative effects, hallucinations, psychosis, changes in mood, impaired cognition, attention, and psychomotor effects,

inappropriate affect, patient dropouts, overdoses; misuse, and lost or unaccounted-for medication and unjustified dose increases). Include time of onset and duration of the event, dose of drug taken, severity and outcome in the narratives. If available, provide pharmacokinetic values for each individual subject who experienced these AEs to understand if there is a temporal correlation between drug plasma levels and AEs. See also section V.B. of the guidance for industry mentioned above.

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[4] and the guidance for industry, *Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER Questions and Answers*[5]. 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*.[6]

4.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

5.0 ACTION ITEMS

There were no action items discussed.

6.0 ATTACHMENTS AND HANDOUTS

Attached is the Division's "General Clinical Safety Requests" document, which was provided with the March 29, 2022, preliminary comments. A copy of the sponsor's April 1, 2022, slide presentation is also attached.

[4] https://www fda.gov/media/84223/download
[5] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/identification-manufacturing-establishments-applications-submitted-cber-and-cder-questions-and
[6] https://www.fda.gov/media/85061/download

Appendix A. General Clinical Safety Requests

1. Datasets:

1. 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.
2. 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.

2. 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 theclinical 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.

3. 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.

4. 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

5. Laboratory and Vital Sign Measurements:

Refer to the following FDA webpage for the CDER position on use of SI units for lab tests: SI Units.[7]

[7] https://www.fda.gov/industry/fda-data-standards-advisory-board/study-data-standards-resources

1. Provide the normal reference ranges for every laboratory value.
2. 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.
3. 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.

4. 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
5. Summarize the protocols for collecting ECG data. Summarize the frequency of post- treatment QTc >450 ms, >480 ms, and >500 ms.

6. 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.

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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/

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