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APPLICATION NUMBER:

761248Orig1s000

OTHER ACTION LETTERS

U.S. FOOD & DRUG ADMINISTRATION

BLA 761248

COMPLETE RESPONSE

Eli Lilly and Company
Attention: Angela Murff-Maxey
Senior Director, Global Regulatory Affairs – NA
Lilly Corporate Center
Drop Code 253
Indianapolis, IN 46285

Dear Ms. Murff-Maxey:

Please refer to your biologics license application (BLA) dated and received on May 18, 2022, and your amendments, submitted under section 351(a) of the Public Health Service Act for Kisunla (LY3002813) injection.

We have completed our review of this application, as amended, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

CLINICAL

The safety database is insufficient to adequately characterize the long-term safety of Kisunla in the treatment of Alzheimer's disease. As stated in the pre-BLA meeting minutes dated November 4, 2021, the Division expected a BLA submission to have at least "100 patients exposed to drug for ≥ 12 months, consistent with ICH E1 guidelines" to adequately characterize the safety of Kisunla for its intended use. Your BLA submission contains data for only 49 patients who were exposed to Kisunla at the highest proposed dosage regimen (700 mg for 3 doses followed by 1400 mg thereafter) for 12 months. We acknowledge that you have tried to meet the exposure requirements through a "treatment protocol" approach based on the dosage regimen of Kisunla specified in the protocol, in which the Kisunla dose was either reduced or stopped when amyloid beta plaque measurements declined to a pre-specified threshold on PET imaging. Under this dosage regimen, some patients were treated with Kisunla for less than 12 months but had continued safety follow-up for a year or longer; however, a substantial number of patients required 12 months or longer of treatment with Kisunla under this dosage regimen. If approved, it is anticipated that there would be a substantial number of patients with Alzheimer's disease who would require treatment for one year or longer. Therefore, the characterization of long-term safety from 100 patients exposed to drug for at least 12 months needs to be based on patients who have had at least 12 months of continued exposure to Kisunla at the highest proposed dosage

regimen. It is also noted that the majority of the 6-month safety exposures are uncontrolled data from open-label studies. A future resubmission intended to adequately characterize the long-term safety of Kisunla would likely need to include the unblinded controlled safety data from Study AACI, once it is completed, as we are not aware of other extant or pending safety data that have the potential to adequately characterize the long-term safety of Kisunla.

See Safety Update section below for additional information on the presentation of your data in a resubmission.

PRESCRIBING INFORMATION

Submit draft labeling that is responsive to our electronic communication dated January 18, 2023.

Prior to resubmitting the labeling, use the SRPI checklist to correct any formatting errors to ensure conformance with the format items in regulations and guidances. In addition, submit updated content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format as described at FDA.gov.

To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Word version. The marked-up copy should include annotations that support any proposed changes.

Your proposed Prescribing Information (PI) must conform to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57. As you develop your proposed PI, we encourage you to review the labeling review resources on the Prescription Drug Labeling Resources and Pregnancy and Lactation Labeling Final Rule[1] 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 in the PI on pregnancy, lactation, and females and males of reproductive potential
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, 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.

- Additional resources for the PI, patient labeling, and carton/container labeling.

CARTON AND CONTAINER LABELING

We reserve comment on the proposed labeling until the application is otherwise adequate.

PROPRIETARY NAME

Please refer to correspondence dated, February 7, 2022, which addresses the proposed proprietary name, Kisunla. This name was found acceptable pending approval of the application in the current review cycle. Please resubmit the proposed proprietary name when you respond to the application deficiencies.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update. The safety update should include data from all nonclinical and clinical studies/trials of the product under consideration regardless of indication, dosage form, or dose level.

(1) Describe in detail any significant changes or findings in the safety profile.

(2) When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

- Present new safety data from the studies/clinical trials for the proposed indication using the same format as in the original submission.

- Present tabulations of the new safety data combined with the original application data.

- Include tables that compare frequencies of adverse events in the original application with the retabulated frequencies described in the bullet above.

- For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

(3) Present a retabulation of the reasons for premature trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.

(4) Provide case report forms and narrative summaries for each subject who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events.

(5) Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original application data.

(6) Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time). Include exposure expressed as subjects exposed to Kisunla 700 mg every 4 weeks for three doses followed by 1400 mg every 4 weeks for 6 months and 12 months, as well for 76, 102, and 130 weeks. Also provide an accounting of the number of subjects who switched to placebo based on amyloid plaque reduction at Weeks 24, 52, 76, 102, and 130.

(7) Provide a summary and analysis of all patients who had recurrent ARIA, including frequency of subjects with multiple episodes of ARIA (e.g., 1, 2, and 3 or more events) and including information regarding patients who were treated through ongoing episodes of ARIA. Include a table with information about individual patients. Include information about whether the patient was asymptomatic or symptomatic (mild, moderate, or severe, if available) and the radiographic severity of ARIA.

(8) Provide a summary and analysis of cases of severe ARIA including information regarding supportive care and whether patients had a full recovery. Include a table with information about individual patients.

(9) Provide a summary of your educational plan to educate prescribers regarding ARIA, to guide prescribers in identifying patients appropriate for Kisunla treatment, and to identify and manage infusion related reactions. Provide a summary of your educational program for patients and caregivers.

(10) Provide a summary of worldwide experience on the safety of this product. Include an updated estimate of use for product marketed in other countries.

(11) Provide English translations of current approved foreign labeling not previously submitted.

ADDITIONAL COMMENTS

We have the following comments/recommendations that are not approvability issues:

PRODUCT QUALITY

1. Include glycosylation profiling in the release specification for Kisunla drug substance using a validated testing method and establish acceptance criteria for main glycan forms, high mannose, and other afucosylated species with upper and lower limits, as applicable. Provide the results of the method validation for glycosylation profiling and the data and analysis used to set acceptance criteria.

OTHER

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 601.3(b)). If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 601.3(c). You may also request an extension of time in which to resubmit the application.

A resubmission must fully address all the deficiencies listed in this letter and should be clearly marked with "**RESUBMISSION**" in large font, bolded type at the beginning of the cover letter of the submission. The cover letter should clearly state that you consider this resubmission a complete response to the deficiencies outlined in this letter. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

You may request a meeting or teleconference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the draft guidance for industry *Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products*.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, contact E. Andrew Papanastasiou, Regulatory Project Manager, by email at emilios.papanastasiou@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Billy Dunn, MD
Director
Office of Neuroscience
Center for Drug Evaluation and Research

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/

WILLIAM H Dunn
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