BLA 761248

BLA APPROVAL

Eli Lilly and Company
Attention: Angela Y. Murff-Maxey
Global Regulatory Sr. Director, North America
Lilly Corporate Center
Indianapolis, IN 46285

Dear Angela Y. Murff-Maxey:

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

We acknowledge receipt of your resubmission dated June 12, 2023, and received June 12, 2023, which constituted a complete response to our January 18, 2023, action letter.

We acknowledge receipt of your major amendment submissions dated July 31, 2023, September 5, 2023, and October 10, 2023, which extended the goal date by three months.

LICENSING

We have approved your BLA for Kisunla (donanemab-azbt) effective this date. You are hereby authorized to introduce or deliver for introduction into interstate commerce, Kisunla under your existing Department of Health and Human Services U.S. License No. 1891. Kisunla is indicated for the treatment of Alzheimer's disease.

MANUFACTURING LOCATIONS

Under this license, you are approved to manufacture donanemab-azbt drug substance at [redacted] (b) (4) The final formulated drug product will be manufactured, filled, labeled, and packaged at [redacted] (b) (4) and labeled and packaged at Eli Lilly and Company Corporate Center, Indianapolis, Indiana. You may label your product with the proprietary name, Kisunla and market it in 350 mg/20 mL single dose vial.

DATING PERIOD

The dating period for Kisunla shall be 24 months from the date of manufacture when stored at 2 °C to 8 °C. The date of manufacture shall be defined as the date of final

sterile filtration of the formulated drug product. The dating period for your drug substance shall be (b) (4) months from the date of manufacture when stored at (b) (4) °C.

FDA LOT RELEASE

You are not currently required to submit samples of future lots of Kisunla to the Center for Drug Evaluation and Research (CDER) for release by the Director, CDER, under 21 CFR 610.2. We will continue to monitor compliance with 21 CFR 610.1, requiring completion of tests for conformity with standards applicable to each product prior to release of each lot.

Any changes in the manufacturing, testing, packaging, or labeling of Kisunla, or in the manufacturing facilities, will require the submission of information to your BLA for our review and written approval, consistent with 21 CFR 601.12.

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, via the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format.[1] Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information and Medication Guide). Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As (October 2009)*.[2]

The SPL will be accessible via publicly available labeling repositories.

CARTON AND CONTAINER LABELING

Submit final printed carton and container labeling that are identical to the carton and container labeling submitted on June 12, 2023, as soon as they are available, but no more than 30 days after they are printed. Please submit the labeling electronically according to the guidance for industry *SPL Standard for Content of Labeling Technical Qs & As.* For administrative purposes, designate this submission "**Final Printed Carton**

[1] See http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm
[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

and Container Labeling for approved BLA 761248." Approval of this submission by FDA is not required before the labeling is used.

REQUESTED ENHANCED PHARMACOVIGILANCE (EPV)

1) We request that for Kisunla you submit all serious and non-serious domestic and/or foreign cases of cerebral hemorrhage greater than 1 centimeter in size that occur in ongoing studies or in the postmarketing setting as well as reports of any deaths in ongoing studies as 15-day "Alert reports" (described under 21 CFR 600.80(c)(1).

2) We request that you provide a narrative summary including analyses of ARIA-E, ARIA-H (specifying microhemorrhage or superficial siderosis), and incident cerebral hemorrhage greater than 1 centimeter in size; serious hypersensitivity reactions; serious infusion reactions; central nervous system vasculitis; intestinal obstruction; and intestinal perforation as part of your required periodic safety reports [e.g., periodic adverse experience report (PAER) required under 21 CFR 600.80(c)(2)], quarterly during the first 3 years post-approval and annually thereafter, through the 10th year following initial U.S. approval date.

Your analyses should include interval and cumulative data relative to the date of approval of Kisunla. Your analyses should provide an assessment of causality, with documentation of indication, temporal association, duration of therapy, associated signs and symptoms, confounders, underlying risk factors, treatment given for the event, outcome, and dechallenge/rechallenge.

Your analyses should include clinical trial cases and postmarketing cases. Include line listings of the cases and individual case safety reports submitted to FAERS in addition to your synthesized summary. The summary should provide an analysis for all subjects and a separate analysis for those in the United States and for those in the rest of the world.

For ARIA and cerebral hemorrhage greater than 1 centimeter in diameter please provide line listings that include:

- Case ID
- Whether the case was a clinical trial case, postmarketing spontaneous report, or postmarketing from a registry
- Age
- Alzheimer's disease stage
- Patient characteristics, including ApoE ε4 genotype if available
- Country where patient is treated
- Concomitant medications
- Time from first Kisunla dose to ARIA
- Listing of dates of Kisunla dosing

- Dates of MRI, including baseline MRI
- Description of MRI findings, including baseline MRI
- Whether patient was symptomatic and if so, list symptoms
- Whether initial finding was symptom or MRI
- Patient outcome (e.g., death, permanent disability, resolved)
- Date of resolution of MRI and of symptoms
- Whether the patient was hospitalized
- Whether and what treatment was received for ARIA
- Whether Kisunla was held, and date that Kisunla dosing resumed
- Whether Kisunla was discontinued
- Specialty of the prescribing physician (e.g., neurologist, psychiatrist, internist).

REQUIRED PEDIATRIC ASSESSMENTS

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.

We are waiving the pediatric study(ies) requirement for this application because necessary studies are impossible or highly impracticable, as Alzheimer's disease only occurs in the adult population.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess the known serious risks of ARIA and of intracerebral hemorrhage greater than 1 cm in patients taking Kisunla.

Furthermore, the active postmarket risk identification and analysis system as available under section 505(k)(3) of the FDCA will not be sufficient to assess these serious risks).

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following studies:

4605-1 Conduct a registry-based, prospective, observational study to evaluate clinical safety outcomes among Alzheimer's disease patients treated with donanemab, using, for example, the Alzheimer's Network for Treatment and Diagnostics (ALZ-NET) registry, including patients who are ApoE ε4 homozygotes, and/or exposed to antithrombotics or thrombolytics, and/or have a diagnosis of, or imaging findings consistent with a high risk for, cerebral amyloid angiopathy. The primary clinical safety outcomes should include amyloid related imaging abnormalities (ARIA)-edema (ARIA-E), and ARIA-hemosiderin deposition (ARIA-H) and any associated clinical symptoms, and intracerebral hemorrhage >1 cm in size. Additional outcomes of interest should also include seizures, anaphylaxis, and death. Baseline characterization of the registry population should include demographic data, diagnosis and stage of disease, ApoE genotype, baseline MRI findings (e.g., microhemorrhages, evidence of cerebral amyloid angiography or other imaging findings consistent with high risk of cerebral amyloid angiography, etc.), other biomarkers that are potential predictors of disease course or adverse outcomes, and prior medications including prior Alzheimer's disease (AD) therapy and antithrombotic therapy. The registry should also collect information on concomitant medications (e.g., antiplatelet and antithrombotic drugs, other AD treatments). When available, the study should provide a comparison of safety outcomes to estimated background rates in an appropriate comparator population.

The timetable you submitted on June 21, 2024, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	04/2025
Final Protocol Submission:	02/2026
Interim/Progress Study Report Submission:	
	08/2026
	02/2027
	08/2027
	02/2028
	08/2028
	02/2029
	08/2029
	02/2030
	08/2030
	02/2031

	08/2031
	02/2032
	08/2032
	02/2033
	08/2033
	02/2034
	08/2034
	02/2035
Study Completion:	02/2036
Final Report Submission:	02/2037

4605-2 Use emerging safety data from ongoing studies and published literature, validate administrative claim codes for intracerebral hemorrhage in patients with Alzheimer's disease. The outcome of intracerebral hemorrhage should distinguish between amyloid related imaging abnormalities-hemosiderin deposition (ARIA-H) and cerebral hemorrhage > 1 cm. Secondary outcomes of interest include ARIA-edema (ARIA-E) and ARIA-H, seizures, anaphylaxis, and death. For secondary outcomes not well validated, develop algorithms and/or computable phenotypes using data leveraged from PMR 4605-1 and other sources for the outcomes of interest. Describe an approach to identifying an appropriate comparator group with Alzheimer disease untreated with donanemab. Obtain FDA agreement with the outcome algorithm specifications and comparator population prior to proceeding to conducting the retrospective cohort study. Based upon validated algorithms agreed to by the Sponsor and FDA, conduct a comparative retrospective cohort study using claims data with available medical chart review as needed or electronic health record data to assess clinical safety outcomes in a broad population of Alzheimer's disease patients treated with donanemab.

The timetable you submitted on June 21, 2024, states that you will conduct this trial according to the following schedule:

Draft Protocol Submission (Algorithm Development):	07/2025
Interim Report Submission (Algorithm Development Final Protocol):	11/2026
Interim Report Submission (Outcome Algorithm):	05/2028
Interim Report Submission (Draft Retrospective Cohort Study Protocol):	02/2029
Final Study Protocol Submission (Retrospective Cohort):	12/2029
Study Completion (Retrospective Cohort):	12/2030
Final Report Submission:	12/2031

FDA considers the term *final* to mean that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial.[3]

Submit clinical protocol(s) to your IND 109157 with a cross-reference letter to this BLA. Submit nonclinical and chemistry, manufacturing, and controls protocols and all final report(s) to your BLA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **Required Postmarketing Protocol Under 505(o), Required Postmarketing Final Report Under 505(o), Required Postmarketing Correspondence Under 505(o).**

Submission of the protocol(s) for required postmarketing observational studies to your IND is for purposes of administrative tracking only. These studies do not constitute clinical investigations pursuant to 21 CFR 312.3(b) and therefore are not subject to the IND requirements under 21 CFR part 312.

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B(a)(1) of the FDCA, as well as 21 CFR 601.70 requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B(a)(1) and 21 CFR 601.70 to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 601.70. We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

[3] See the guidance for Industry *Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (October 2019).* https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

4605-3 Conduct a randomized, double-blind, controlled trial of donanemab in participants with early-stage Alzheimer's disease. All participants should receive an initial dosing regimen in which dosing is stopped based on reduction of amyloid, followed by randomization to either a maintenance dose(s) of donanemab or placebo for a period of at least 2 years. The primary efficacy endpoint will be the Clinical Dementia Rating scale. The study should also collect biomarkers of Alzheimer's disease pathology. This trial may be conducted through cross over of participants in TRAILBLAZER-ALZ 3 upon completion of that trial.

The timetable you submitted on June 25, 2024, states that you will conduct this study according to the following schedule:

Draft Protocol Submission: 10/2024
Final Protocol Submission: 06/2025
Study/Trial Completion: 12/2030
Final Report Submission: 10/2031

POSTMARKETING COMMITMENTS NOT SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

4605-4 Conduct adequate analytical validation testing to establish and support labeling of an FDA cleared or approved in vitro diagnostic device to accurately and reliably detect ApoE e4 alleles that is safe and effective for identifying patients at increased risk of ARIA if treated with Kisunla. The results of the validation studies are intended to inform product labeling.

The timetable you submitted on June 21, 2024, states that you will conduct this study according to the following schedule:

Final Report Submission: 07/2026

Submit clinical protocols to your IND 109157for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this BLA. In addition, under 21 CFR 601.70 you should include a status summary of each commitment in your annual progress report of postmarketing studies to this BLA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical

studies/trials, number of patients/subjects entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled "**Postmarketing Commitment Protocol**," "**Postmarketing Commitment Final Report**," or "**Postmarketing Commitment Correspondence**."

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. For information about submitting promotional materials, see the final guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format-Promotional Labeling and Advertising Materials for Human Prescription Drugs*.[4]

You must submit final promotional materials and Prescribing Information, accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at FDA.gov.[5] Information and Instructions for completing the form can be found at FDA.gov.[6]

REPORTING REQUIREMENTS

You must submit adverse experience reports under the adverse experience reporting requirements at 21 CFR 600.80.

Prominently identify all adverse experience reports as described in 21 CFR 600.80.

You must submit distribution reports under the distribution reporting requirements at 21 CFR 600.81.

You must submit reports of biological product deviations under 21 CFR 600.14. You should promptly identify and investigate all manufacturing deviations, including those associated with processing, testing, packing, labeling, storage, holding and distribution. If the deviation involves a distributed product, may affect the safety, purity, or potency of the product, and meets the other criteria in the regulation, you must submit a report on Form FDA 3486 to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Compliance Risk Management and Surveillance
5901-B Ammendale Road
Beltsville, MD 20705-1266

[4] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/media/128163/download.
[5] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[6] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf

Biological product deviations, sent by courier or overnight mail, should be addressed to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Compliance Risk Management and Surveillance
10903 New Hampshire Avenue, Bldg. 51, Room 4207
Silver Spring, MD 20903

POST APPROVAL FEEDBACK MEETING

New biological products qualify for a post approval feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

If you have any questions, contact me at 1-(301)-837-7650 or via email Justine.Kankam@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

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

ENCLOSURE(S):

- Content of Labeling
  - Prescribing Information
  - Medication Guide

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/

TERESA J BURACCHIO
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