CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761248Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 109157

CORRECTION: MEETING MINUTES

Eli Lilly and Company
Attention: Angela Murff-Maxey
Adviser - Global Regulatory Affairs
Lilly Corporate Center
Drop Code 2543
Indianapolis, IN 46285

Dear Ms. Murff-Maxey:[1]

Please refer to your Investigational New Drug Application (IND) submitted under Section 505(i) of the Federal Food, Drug, and Cosmetic Act for LY3002813.

We also refer to the teleconference between representatives of your firm and the FDA on August 26, 2021. The purpose of the meeting was to discuss your proposed Biologics License Application (BLA) for LY3002813.

We further refer to our Preliminary Comments dated August 25, 2021, and to our Meeting Minutes dated October 7, 2021.

It has come to our attention that there was an error in the October 7, 2021, Meeting Minutes. The clinical pharmacology and safety appendices (labeled “Attachment I” and “Attachment II,” respectively) that were attached to the Preliminary Comments dated August 25, 2021, were inadvertently excluded from the October 7, 2021, Meeting Minutes. The purpose of this letter is to provide the meeting minutes with the addition of these two attachments. No other changes, as compared to the October 7, 2021, Meeting Minutes, have been made.

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.

[1] 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.

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}

Eric Bastings, MD
Director (Acting)
Division of Neurology 1
Office of Neuroscience
Center for Drug Evaluation and Research

Enclosure:

- Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: Pre-BLA

Meeting Date and Time: August 26, 2021, from 11:00 AM to 12:00 PM ET
Meeting Location: By Teleconference

Application Number: IND 109157
Product Name: Donanemab (LY3002813)
Indication: Alzheimer's disease
Sponsor Name: Eli Lilly and Company
Regulatory Pathway: 351(a)

FDA ATTENDEES

Office of New Drugs

Peter Stein, MD	Director, Office of New Drugs

Office of Neuroscience

Billy Dunn, MD	Director, Office of Neuroscience
Eric Bastings, MD	Deputy Director, Office of Neuroscience Director (Acting), Division of Neurology 1
Michelle Campbell, PhD	Stakeholder Engagement and Clinical Outcomes

Division of Neurology 1

Teresa Buracchio, MD	Deputy Director, Division of Neurology 1 (DN1)
Ranjit Mani, MD	Clinical Team Leader, DN1
Kevin Krudys, PhD	Senior Clinical Analyst, DN1
Deniz Erten-Lyons, MD	Clinical Reviewer, DN1
Sally Jo Yasuda, PharmD, MS	Clinical Safety Team Leader
Kun Jin, PhD	Biostatistics Team Leader
Tristan Massie, PhD	Biostatistical Reviewer
Haoheng Yan, PhD	Biopharmaceutics Team Leader
Rukman De Silva, PhD	Biopharmaceutics Reviewer
Sic Chan, PhD	Scientific Reviewer, CDRH
Yifei Zhang, PhD	Clinical Pharmacology Reviewer
Bilal AbuAsal, PhD	Clinical Pharmacology Team Leader

Atul Bhattaram, PhD	Pharmacometrics Team Leader
Lois Freed, PhD	Supervisory Toxicologist
David Hawver, PhD	Nonclinical Reviewer
E. Andrew Papanastasiou, MS, PharmD	Senior Regulatory Project Manager, Division of Regulatory Operations for Neuroscience

SPONSOR ATTENDEES

Mark Mintun	Vice President, Pain and Neurodegeneration
David Bradley Woodward	Vice President, Global Patient Safety
Dawn Brooks	Global Brand Development Leader
John Sims	Senior Medical Director
Elizabeth Ann Van Sant Hoffman	Senior Director, Clinical Development
JonDavid Sparks	Research Advisor, Statistics
Carl Garner	Vice President, Global Regulatory Affairs
Stephen Truocchio	Senior Director, Global Regulatory Affairs
Angela Murff-Maxey	Advisor, Global Regulatory Affairs
Paul Ardayfio	Research Advisor, Global Patient Safety
Lisa Wenzler	Senior Research Advisor, Global Regulatory CMC

1.0 BACKGROUND

This Pre-Biologics License Application (Pre-BLA) meeting package seeks the Agency's advice regarding the proposed format and content of a BLA for donanemab (LY3002813) for the treatment of Alzheimer's disease. This BLA is to be submitted under the accelerated approval regulations (21 CFR part 601, subpart E).

Donanemab is a humanized IgG1 monoclonal antibody directed specifically against an N-terminal truncated and pyroglutamate-modified Aβ peptide 3-42.

A Phase 2 randomized, double-blind, placebo-controlled, parallel-arm study I5T-MC-AACG (AACG; TRAILBLAZER-ALZ) of donanemab has been completed and a further Phase 2 randomized, double-blind, placebo-controlled, parallel-arm study I5T-MC-AACI (AACI; TRAILBLAZER-ALZ2) of donanemab is ongoing. A Phase 2 follow-on study I5T-MC-AACH (AACH; TRAILBLAZER-EXT) of donanemab is also ongoing. Studies AACG and AACI have both enrolled patients with early Alzheimer's disease.

Two Phase 1 studies of donanemab, I5T-MC-AACC (AACC) and I5T-MC-AACD (AACD) have also been completed

As noted above, the sponsor proposes, in the initial BLA submission, to seek the approval of donanemab for the treatment of Alzheimer's disease under the accelerated

approval regulations. Under that proposal, Study AACG is to be an adequate and well-controlled study in which evidence of an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit, i.e., a reduction in brain amyloid plaques on positron emission tomography, has been demonstrated. The completed studies AACC and AACD are to provide supportive evidence of the efficacy of donanemab in Alzheimer's disease.

The clinical safety data for donanemab proposed to be included in the initial BLA submission are to be drawn from the completed studies AACH, AACC, and AACD, combined with unblinded data from the ongoing study AACI. Some preliminary discussion of the clinical safety data to be submitted in the proposed BLA has already taken place at a teleconference between the Agency and sponsor on July 20, 2021.

The nonclinical and clinical pharmacology data proposed to be included in the initial BLA submission for donanemab are also summarized in the meeting package. The Chemistry, Manufacturing, and Controls (CMC) data proposed to be submitted as part of the initial BLA have already been discussed at a CMC-only Pre-BLA meeting with the sponsor on August 6, 2021.

Donanemab has been granted Fast Track and Breakthrough Designation by the Agency.

FDA sent Preliminary Comments to Eli Lilly and Company on August 25, 2021.

2.0 DISCUSSION

Question 1: Does FDA agree that the nonclinical data package, described in Section 5, is sufficient to support review?

FDA Response to Question 1:
We agree that the nonclinical data described in Section 5 of this meeting package are sufficient to support review of the proposed BLA.

Meeting Discussion:
None.

Question 2: Primary efficacy data for the proposed application under accelerated approval is provided by a single adequate and well-controlled study demonstrating a robust effect showing a reduction of amyloid plaques as a surrogate endpoint reasonably likely to predict clinical benefit, with supportive efficacy data provided by Phase 1. Does FDA agree that the planned clinical data package (described in Section 6.2) is sufficient to support review?

FDA Response to Question 2:
The proposed efficacy data described in Section 6.2 appear sufficient, in form, to support the submission of a marketing application for donanemab under the accelerated approval regulations; however, please refer to our response to Question 5 regarding our concerns about the proposed safety database.

Meeting Discussion:
None.

Question 3: Does FDA agree that the clinical pharmacology package (described in Section 6.3) is sufficient to support review?

FDA Response to Question 3:
Our comments below address the clinical pharmacology package to be included in your proposed BLA for donanemab.

- You state that the amyloid imaging and clinical results are further supported by analyses using a prespecified Bayesian disease progression model and exploratory natural cubic spine and quadratic models, as well as analyses of imaging and blood biomarkers for tau. We recommend that you submit details of these models and analyses to facilitate the review of your BLA.

- Please refer to the attachment at the end of this document, entitled "*Clinical Pharmacology Summary Aid*," when preparing your BLA.

- We also have the following comments regarding your planned assessment of the effect of the immunogenicity of donanemab on pharmacokinetics, pharmacodynamics, safety, and efficacy:

  - You indicate that no statistically significant relationship exists between anti-drug antibody (ADA) titer and time to first amyloid related imaging abnormality-edema (ARIA-E) event. (b) (4) [redacted] For your assessments of the effect of the immunogenicity of donanemab on pharmacokinetics, pharmacodynamics, safety, and efficacy, we strongly recommend that you address the effect size.

  - You indicate, based on your analyses, that ADA titers generally peak between 16 and 40 weeks after the first dose of donanemab and subsequently decline; however, it is unclear whether immunogenicity was treated as a time-varying covariate in those assessments. We strongly encourage you to assess the relationship of time-dependent immunogenicity measurements (i.e., the time

profile of that ADA titer) with clinical outcomes and biomarker measurements. You may consider stratifying clinical outcomes and biomarker measurements by early ADA onset or late ADA onset. For example, subjects that become ADA-positive during the first week of treatment are expected to be impacted differently by immunogenicity than subjects who become ADA-positive for the first time during the last week of treatment. This will help explain the study findings considering the time-varying nature of the formation of ADA and their role in increasing clearance of donanemab.

Meeting Discussion:
None.

Question 4: Understanding that labeling is a review matter, does FDA have initial feedback on the proposed indication and dosing instructions presented in Section 6.4, as they may relate to the proposed clinical presentations in the BLA?

FDA Response to Question 4:
We are not able to provide feedback on your proposed indication or dosing instructions at this time. Labeling discussions will require review of the data in your BLA submission.

Meeting Discussion:
None.

Question 5: Does FDA agree with the proposal outlined in Section 6.6 to provide an appropriate and adequate safety evaluation based on AACC, AACD and AACG and separate outputs based on ongoing Study AACI, at the time of the initial BLA?

FDA Response to Question 5:
As previously discussed in our preliminary meeting responses that were provided to you by email on July 19, 2021, and briefly discussed at the meeting held on July 20, 2021, an adequate characterization of the safety profile of donanemab needs to be provided with the initial BLA submission. The safety data from Studies AACG, AACD, and AACC do not provide an adequate database to characterize the safety of donanemab given the limited exposure in those studies.

We have considered your proposal to provide unblinded safety data from Study AACI by leveraging data outputs produced for the Data Monitoring Committee for that study and have determined that such data will not be of adequate quality to characterize the safety of donanemab in support of a marketing application. Cleaned and quality-controlled safety datasets of typical character are necessary for the Agency to perform an adequate review of safety. Additionally, although we understand that your proposed approach is intended to maintain the blind for study staff, available safety data need to be evaluated and presented in an integrated safety summary (ISS) in order to inform your risk-benefit analysis, particularly for an

assessment of the known risk of amyloid-related imaging abnormalities (ARIA) or other unanticipated risks that may be associated with donanemab. Similarly, it is also unclear if the Independent Safety Review Committee (ISRC) chairperson or team would be adequate or appropriate to handle discussions of safety that could impact labeling or risk-benefit conclusions.

Further, the unblinded safety data would need to be appropriately incorporated in the NDA submission with comprehensive safety analyses reflected in the ISS (e.g., in pooled safety analyses, in narratives, and in submitted data tabulations) and study reports to support our comprehensive analysis of safety. Unblinding to provide that level of detail, including staff that could respond to information requests regarding the safety findings, would require you to unblind Study AACI with a firewalled team. We strongly discourage such a step, given the risks to study integrity which could raise concerns during our subsequent review of the study, and also potentially hamper broader public acceptance of the results of a study unblinded by the company prior to study completion.

For these reasons, the current proposal to provide unblinded safety data from Study AACI is not adequate.

Meeting Discussion:

The sponsor noted the Agency's preliminary response to this question and presented a proposal to address them. Under that proposal, Study AACI would consist of 2 consecutive cohorts, Cohort 1 and Cohort 2. Cohort 1 would consist of the initial 300 patients to be enrolled in that study; the safety data for that cohort would be unblinded with those data to be then included in the original BLA submission. Cohort 2 would consist of the remaining 1000 patients enrolled in Study AACI; the efficacy data for Cohort 2 would be used for the primary efficacy analysis when the study is complete. Efficacy analyses would be conducted on Cohort 1 as a stand-alone cohort, and also combined with Cohort 2 at completion of study as prospectively defined analyses. Further details of that proposal were provided by the sponsor at the meeting, including how the blind for Cohort 2 would be maintained when the blind for Cohort 1 is broken. The sponsor further indicated that the overall timelines for Study AACI would not be altered by that proposal. The Agency expressed several concerns about that proposal, including whether the overall integrity of the study would be preserved. Further concerns expressed by the Agency were as follows: whether randomization for Cohort 2 would be preserved as it was when the study began; whether the effects of donanemab in Cohort 1 might not be quite the same as they are for Cohort 2; and the creation of Cohort 2 would be somewhat arbitrary. The Agency was also concerned at the possibility that multiplicity might compromise the efficacy analyses for the two consecutive cohorts, but the sponsor indicated that only a single primary efficacy analysis (that for Cohort 2) would be performed.

Given the complexity of the sponsor's proposal for addressing the Agency's concerns about the safety database for the proposed BLA for donanemab, the Agency was unable to comment more substantively about that proposal during the meeting. The Agency therefore asked that the sponsor submit that proposal in full after the meeting, and agreed to provide comments on that proposal as a post-meeting response to be included in the Agency's meeting minutes.

Post-Meeting Comments:
The Division wishes to clarify that although it inadvertently referred to Tables 3.4 and 3.8 in the meeting package submitted on July 2, 2021, Tables 6.4 and 6.6 in the submission dated July 30, 2021, were those actually reviewed and were the basis for the comments and conclusions from the Division at the meeting.

As requested by the Agency at the meeting, the sponsor submitted a detailed proposal for addressing the Agency's concerns about the proposed safety database for donanemab at the time of submission of the initial BLA. The proposal was submitted to this IND on August 30, 2021, under Serial #153. The Agency's response to that proposal is below.

We continue to have substantial concerns regarding both the perception and the potential for the unblinding of an ongoing clinical trial to impact study integrity, particularly given that Study AACI is a large trial of particular importance to your development plans. We note that your submission lacks details on the process for unblinding of the study (e.g., details of who will be unblinded, and how the firewall will be maintained). However, regardless of those details and no matter how carefully executed, unblinding data from an ongoing study always raises concerns about the impact of such unblinding on study integrity. There is potential for perceived and actual untoward bias, with compromise to data integrity, including complications that may not yet be foreseen, even with planning for a firewall. For any subsequent submissions based on data from Study AACI, the Agency would require adequate reassurance that there has been no impact on study integrity based on the unblinding.

Additionally, we do not agree that the proposed safety database for the initial BLA submission is sufficient to adequately characterize the safety of donanemab, particularly for exposures ≥ 6 months and ≥ 12 months. We would expect the initial BLA submission to have at least 300 patients exposed to drug for ≥ 6 months and 100 patients exposed to drug for ≥ 12 months, consistent with ICH E1 guidelines. The numbers for the safety update (Table 6.6) proposed to be submitted on February 15, 2022 (based on a January 15, 2022, data cutoff), are more consistent with what we would expect to be included in an initial BLA submission.

Therefore, we are concerned that your proposal to provide safety data from AACI will not be adequate at the time of submission that you have proposed to support a marketing application for donanemab.

Question 6: Does FDA agree with the proposed approach to the post-submission safety update (described in Section 6.7)?

FDA Response to Question 6:
Please see our response to Question 5.

Meeting Discussion:
Please see the meeting discussion and post-meeting comments under Question 5.

Question 7: Does FDA agree that the planned contents of the BLA constitute a complete application for the proposed indication?

FDA Response to Question 7:
Please see our responses to Questions 2, 3, and 5.

As you know, part of the data package for your proposed BLA has already been discussed at a CMC-only Pre-BLA meeting held on August 6, 2021. At that meeting, you had proposed a new CMC data submission plan. Subsequently, you provided additional clarification on the drug product process performance qualification (PPQ) strategy, commercial production plan, and data availability timetable. The Agency has provided final post-meeting comments regarding your CMC data submission plan and the planned contents of the CMC data package for your BLA in the final minutes of the CMC-only Pre-BLA meeting.

In addition, we have the following comments regarding the proposed Table of Contents for the planned BLA for donanemab, as provided in Appendix 1 of this meeting package.

- All documents included under Section 3.2.A (Appendices) must be placed in one of the specified sub-folders within 3.2.A as shown below:

    - 3.2.A.1 Facilities and Equipment [name, manufacturer].
    - 3.2.A.2 Adventitious agents safety evaluation [name, dosage form, manufacturer].
    - 3.2.A.3 Novel excipients.

    The currently-proposed Table of Contents has all documents located in Section 3.2.A, but not in any sub-folders.

- Section 5.3.5.1 is incorrectly titled "*Reports of Efficacy and Safety Studies*". Section 5.3.5.1 should instead be titled "*Study Reports and Related Information for Controlled Clinical Studies Pertinent to the Claimed Indication*" which is a sub-folder of 5.3.5 "*Reports of Efficacy and Safety Studies*."
- From a technical perspective only, unrelated to content, all other sections of the Proposed Table of Contents are acceptable.

Please also refer to the following Agency publications for more details of each module and section:

- The publication entitled "*Comprehensive Table of Contents Headings and Hierarchy*" publication available at:

  https://www.fda.gov/media/76444/download

- The publication entitled "*M4 Organization of the Common Technical Document for Registration of Pharmaceuticals for Human Use Guidance for Industry*" available at:

  https://www.fda.gov/media/71551/download

Meeting Discussion:
None.

Question 8: Rolling submission - pending the outcome of the 06 August 2021 pre-BLA CMC meeting, and the response to Question 5, does FDA agree to the rolling submission plan outlined in Section 8.

FDA Response to Question 8:
In general, a rolling submission is acceptable for donanemab, as it has breakthrough designation; however, we refer you to the response to Question 5 regarding your proposal for the submission of safety data.

Meeting Discussion:
The sponsor is to submit a request for a rolling submission and review.

Question 9: Does FDA agree that aducanumab does not constitute available therapy per FDA expedited programs guidance (see Section 8) and therefore, for the purposes of a priority review designation, justification that donanemab represents a significant improvement in safety or effectiveness over existing therapy is not required?

FDA Response to Question 9:
A request for priority review of your application will be considered at the time of filing. A request for priority review needs to include a description of how your product addresses an unmet need compared to available therapy. As described in the Guidance for Industry entitled: "*Expedited Programs for Serious Conditions – Drugs and Biologics*,"[2] a drug would not be considered available therapy if the drug is granted accelerated approval based on a surrogate endpoint or an intermediate clinical endpoint and clinical benefit has not been verified by post-approval studies.

[2] https://www.fda.gov/media/86377/download

Meeting Discussion:
None.

Question 10: Does the FDA anticipate the need for an application orientation meeting to be scheduled?

FDA Response to Question 10:
The Division is open to a request from you for an application orientation meeting. The need for that meeting will be considered after your application has been submitted.

Meeting Discussion:
None.

Question 11: Does the FDA anticipate the need to convene an Advisory Committee during review of this BLA?

FDA Response to Question 11:
An Agency determination regarding the need for an Advisory Committee meeting will be made after filing and during review of your complete marketing application.

Meeting Discussion:
None.

3.0 ADDITIONAL INFORMATION

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

As stated in our July 13, 2021, communication granting this meeting, if, at the time of submission, the application that is the subject of this meeting is for a new molecular entity or an original biologic, the application will be subject to "the Program" under PDUFA VI. Therefore, at this meeting be prepared to discuss and reach agreement with FDA on the content of a complete application, including preliminary discussions on the need for risk evaluation and mitigation strategies (REMS) or other risk management actions and, where applicable, the development of a Formal Communication Plan. You and FDA may also reach agreement on submission of a limited number of minor application components to be submitted not later than 30 days after the submission of the original application. These submissions must be of a type that would not be expected to materially impact the ability of the review team to begin its review. All major components of the application are expected to be included in the original application and are not subject to agreement for late submission.

Discussions and agreements will be summarized at the conclusion of the meeting and reflected in FDA's meeting minutes. If you decide to cancel this meeting and do not

have agreement with FDA on the content of a complete application or late submission of any minor application components, your application is expected to be complete at the time of original submission.

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

Information on the Program is available at FDA.gov.[3]

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*.[4] 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 FDA.gov.[5]

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[3] https://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/default.htm
[4] When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.
[5] https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development

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 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.

When the safety data are submitted with the BLA, please refer to the standard safety requests in Attachment 2.

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]

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:

[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.

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 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]

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

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

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 1.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

The sponsor provided clarifications to the planned BLA safety database for donanemab, following the Pre-BLA meeting, with a request for further guidance from the Division.

5.0 ACTION ITEMS

None.

6.0 ATTACHMENTS AND HANDOUTS

ATTACHMENT I

CLINICAL PHARMACOLOGY SUMMARY AID

1. Goal

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

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

2. Question Based Review

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

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

2.2 General Attributes of the Drug

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

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

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

2.2.3 What are the proposed dosages and routes of administration?

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

2.3 General Clinical Pharmacology

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

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

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

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

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

Indicate circulating active moieties and their plasma and-tissue concentration range after therapeutic doses of the drug of interest. Provide evidence that sensitivity of the assay method(s) used is (are) sufficient to determine apparent terminal t1/2 and AUC.

2.4 Exposure-Response

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

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

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

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

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

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

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

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

2.4.3 Does this drug prolong QT/QTc Interval?

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

drug of interest at supra-therapeutic levels is different from that at therapeutic levels.

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

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

2.5 What are the PK characteristics of the drug?

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

Briefly describe methods (two-stage and/or population approaches, compartment model dependent or-independent methods) in healthy subjects and in patients with the target disease used to determine the pharmacokinetic parameters of parent drug and relevant metabolites (pharmacologically active or impacting the exposure to parent drug or co-administered drugs). Provide mean, median (SD, CV%) pharmacokinetic parameters of parent drug and relevant metabolites after single doses and multiple doses at steady-state [Cmax, tmax, AUC, Cmax,ss, Cmin,ss, Cmax,ss/Cmin,ss, tmax,ss, AUC0-τ, CL/F, V/F and t1/2 (half-life determining accumulation factor), accumulation factor, fluctuation, time to steady-state]. Indicate how attainment of steady-state is determined. Provide evidence for attainment of steady-state.

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

Compare the pharmacokinetic parameters of the drug of interest and relevant metabolites in healthy subjects and patients with the target disease. Provide a rationale for observed significant differences between healthy subjects and patients with the target disease.

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

Provide mean/median (SD, coefficient of variation, range within 5% to 95% confidence interval bracket for concentrations) about mean AUC, Cmax, Cmin, CL/F and t1/2 of the parent drug and relevant metabolites after single doses and at steady-state.

2.5.4 What are the characteristics of drug absorption?

Indicate absolute and relative bioavailability, lag time, tmax, tmax,ss, Cmax, Cmax,ss and extent of systemic absorption of parent drug and relevant

metabolites in healthy subjects and patients with the target disease. Indicate mean (SD) for these parameters.

2.5.5 What are the characteristics of drug distribution?

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

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

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

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

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

2.5.8 What are the characteristics of drug metabolism?

Present the metabolic scheme for the drug. Provide an estimate for the contribution of metabolism to the overall elimination of the drug of interest. Indicate mean (SD) values for the non-renal clearance in healthy subjects and patients with the target disease. Indicate whether active metabolites constitute major circulating moieties and if so how much they contribute to effectiveness and/or whether they affect safety.

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

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

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

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

2.5.11 What are the characteristics of drug excretion in urine?

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

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

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

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

Indicate whether the mean ratio of AUC0-τ at steady-state to AUC after the first dose for the circulating major active moieties deviates statistically significantly from 1.0 in healthy subjects and patients with the target disease. Discuss the relevance of the findings and indicate whether an adjustment of the dose regimen is required. If the pharmacokinetics of the drug of interest changes with time provide a rationale for the underlying mechanism.

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

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

2.6 Intrinsic Factors

2.6.1 What are the major intrinsic factors responsible for the inter-subject variability in exposure (AUC, Cmax, Cmin) in patients with the target

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

Provide mean (SD) parameters for AUC, Cmax, clearance, volume of distribution and t1/2 for pairs studied (e.g. elderly vs. young, male vs. female, normal body weight vs. obese, race/ethnicity(x) vs. race/ethnicity (y), mild vs. severe target disease)

2.6.2 Based upon what is known about E-R relationships in the target population and their variability, what dosage regimen adjustments are recommended for each group?
Characterize the populations (age, sex, body weight, ethnicity/race) used to determine the impact of each intrinsic factor on variability in exposure and exposure-response. Indicate for each intrinsic factor whether a dose adjustment (change of dose or dose interval or both)) is required or not and provide a rationale for either scenario.

2.6.2.1 Severity of Disease State

2.6.2.2 Sex

2.6.2.3 Body Weight

2.6.2.4 Elderly

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

2.6.2.6 Race/Ethnicity

2.6.2.7 Renal Impairment

Characterize the demographics for each subgroup (normal renal function, mild, moderate and severe renal impairment, on and off dialysis). Indicate mean (SD, range) for creatinine clearance estimated by the Cockroft-Gaul- and MDRD equations for the stages of renal impairment investigated. Provide arithmetic mean (SD) AUC, Cmax and t1/2 of parent drug and relevant metabolites in the different sub-groups assessed by 2-stage or population PK approaches. Show regressions including 90% confidence intervals of AUC, Cmax and CL/F on Clcr for parent drug and relevant metabolites. If a population approach is used provide evidence supporting that statistical power was sufficient to determine impact of creatinine clearance.

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

2.6.2.8 Hepatic Impairment

Characterize the demographics for each subgroup (normal hepatic function, mild, moderate and severe hepatic impairment based on Child-Pugh scores). Provide information on arithmetic mean (SD) AUC, Cmax, tmax and t1/2 of parent drug and relevant metabolites in the different hepatic function sub-groups assessed by two-stage or population PK approaches. Show regressions including 90% confidence intervals of Cmax, AUC or CL/F on the Child-Pugh score for parent drug and relevant metabolites. Indicate whether plasma protein binding of the active moieties is significantly altered in hepatic impairment and whether the change in the unbound fraction is clinically relevant. Indicate whether a dose adjustment is required or not for each of the subgroups of patients with impaired hepatic function and provide a rationale for either scenario. If a population approach is used provide evidence supporting that statistical power was sufficient to determine impact of Child-Pugh score.

2.6.2.9 What pregnancy and lactation use information is available?

2.6.3 Does genetic variation impact exposure and/or response?

Describe the studies in which DNA samples have been collected. If no DNA samples were collected state so. Include a table with links to the studies in which DNA was analyzed and genomic/genetic information is reported. In the description of these studies include demographics, purpose of DNA analysis (effectiveness, safety, drug metabolism, rule in-out of patients, etc.), rationale for the analysis, procedures for bio-specimen sample collection and DNA

isolation, genotyping methods, genotyping results in individual subjects, statistical procedures, genotype-phenotype association analysis and results, interpretation of results, conclusions. If genomic polymorphism impacts either exposure and/or response indicate the measures to be taken to safeguard efficacy and safety of the drug in subjects with varying genotypes. Indicate the contribution of genetic factors to inter-subject variability.

2.6.4 Immunogenicity (NOT applicable to small molecule drugs)

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

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

2.6.4.3 Do the anti-product antibodies have neutralizing activity?

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

2.6.4.5 What is the impact of anti-product antibodies on clinical safety?
Provide information on the incidence of infusion-related reactions, hypersensitivity reactions, and cross-reactivity to endogenous counterparts.

2.7 Extrinsic Factors

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

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

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

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

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

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

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

2.7.6 What extrinsic factors influence exposure and/or response, and what is the impact of any differences in exposure on effectiveness or safety responses?

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

2.7.7 What are the drug-drug interactions?

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

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

Provide information on the demographics of populations, number of subjects, dose levels, and design of the studies performed in humans. Justify the magnitude of the equivalence interval selected if it is greater than the default interval. Report t1/2, point estimates and 90% confidence intervals of the geometric mean ratios of AUC and Cmax for the drug of interest in the presence and absence of each of the co-administered drugs. Provide a summary statement on the drug interaction liability of the drugs as victim. Indicate whether a dose adjustment is required or not. In either case provide a rationale. Define the required adjusted dose regimens.

b) Drug of interest impacts other co-administered drugs

Provide information on the demographics of populations, number of subjects, dose levels, and design of the studies performed in humans. Justify the magnitude of the equivalence interval selected if it is greater than the default interval. Provide a summary statement on the drug interaction liability of the drug as a perpetrator. Report t1/2, point estimates and 90% confidence intervals of the geometric mean ratios of AUC and Cmax for each of the co-administered drugs in the presence and absence of the drug of interest.

2.7.8 Does the label specify co-administration of another drug?

2.7.9 What other co-medications are likely to be administered to the target population?

2.7.10 Is there a known mechanistic basis for pharmacodynamic drug-drug interactions?

2.8 General Biopharmaceutics

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

IR Product

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

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

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

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

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

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

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

MR product (if an IR is already marketed)

2.8.6 What is the bioavailability of the MR product relative to the approved IR product? How does the plasma concentration time profile of the MR formulation compare to that of the IR formulation after single and multiple doses?
Indicate whether or not the pharmacokinetics of the drug of interest is linear, dose proportional or nonlinear after administration of the MR formulation. Summarize data on Cmax, AUC and Cmin of the IR and MR formulations after a single dose and multiple doses at steady-state. Provide information on the fluctuation factor at steady-state.

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

2.8.8 What is evidence that MR formulation displays less variability in Cmax, AUC and Cmin than IR formulation?

2.8.9 Does the MR product show dose dumping *in vivo*?
Describe design, demographics and number of subjects participating in the studies performed to determine whether dose dumping occurs with the MR

formulation when given in the fed state or when given together with alcohol. Present summaries of results.

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

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

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

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

2.9 Analytical Section

2.9.1 How are parent drug and relevant metabolites identified and what are the analytical methods used to measure them in plasma and other matrices?
List all assays used and briefly describe the individual methods.

2.9.2 Which metabolites have been selected for analysis and why?

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

2.9.4 What bioanalytical methods are used to assess concentrations of the measured moieties?
Identify all studies that used a particular assay method. For each assay report indicate the corresponding assay validation report.

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

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

2.9.5.1 What are the lower and upper limits of quantitation?
For each method and analyte indicate LLOD, LLOQ and ULOQ for undiluted and diluted samples.

2.9.5.2 What are the accuracy, precision, and selectivity at these limits?
For each method and analyte indicate inter-day and intra-day precision (CV%) and inter-day and intra-day accuracy (RE%).

2.9.5.3 What is the sample stability under conditions used in the study?
For all studies in which concentrations of the drug of interest and relevant metabolites were measured provide information on initiation date of study, date of last sample analyzed and total sample storage time. For each method and matrix provide information on the stability of the analytes, i.e. number of freeze-thaw cycles, benchtop stability at room temperature and stability during long term storage at ≤ –20° C.

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

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

Applicable to therapeutic proteins only

2.9.5.6 What bioanalytical methods are used to assess therapeutic protein concentrations?
Briefly describe the methods and summarize the assay performance.

2.9.5.7 What bioanalytical methods are used to assess the formation of the anti-product antibodies?
Briefly describe the methods and assay performance including sensitivity, specificity, precision, cut point, interference and matrix, etc.

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

ATTACHMENT II

Attachment II.

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

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.

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/

TERESA J BURACCHIO on behalf of ERIC P BASTINGS
11/04/2021 11:17:59 AM

IND 109157

MEETING MINUTES

Eli Lilly and Company
Attention: Stephen P. Truocchio, MS, RAC
Senior Director - Global Regulatory Affairs
Lilly Corporate Center
Drop Code 2543
Indianapolis, IN 46285

Dear Mr. Truocchio:[1]

Please refer to your Investigational New Drug Application (IND) submitted under Section 505(i) of the Federal Food, Drug, and Cosmetic Act for donanemab (LY3002813).

We also refer to the teleconference between representatives of your firm and the FDA on July 20, 2021. The purpose of the meeting was to discuss the development plan for donanemab.

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

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}

Eric Bastings, MD
Director (Acting)
Division of Neurology 1
Office of Neuroscience
Center for Drug Evaluation and Research

Enclosure:

- Meeting Minutes

[1] 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.

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: End of Phase 2

Meeting Date and Time: July 20, 2021 from 9:00 AM to 11:00 AM
Meeting Location: By Teleconference

Application Number: IND 109157
Product Name: Donanemab (LY3002813)
Indication: Alzheimer's Disease
Sponsor Name: Eli Lilly and Company
Regulatory Pathway: 351(a)

FDA ATTENDEES

Office of Neuroscience

Billy Dunn, MD	Director, Office of Neuroscience
Eric Bastings, MD	Deputy Director, Office of Neuroscience Director (Acting), Division of Neurology 1
Michelle Campbell, PhD	Stakeholder Engagement and Clinical Outcomes

Division of Neurology 1

Teresa Buracchio, MD	Deputy Director, Division of Neurology 1 (DN1)
Ranjit Mani, MD	Clinical Team Leader, DN1
Kevin Krudys, PhD	Senior Clinical Analyst, DN1
Deniz Erten-Lyons, MD	Clinical Reviewer, DN1
Sally Jo Yasuda, PharmD, MS	Clinical Safety Team Leader
Gerald Boehm, MD, MPH	Clinical Safety Reviewer
Kun Jin, PhD	Biostatistics Team Leader
Tristan Massie, PhD	Biostatistical Reviewer
Haoheng Yan, PhD	Biopharmaceutics Team Leader
Rukman De Silva, PhD	Biopharmaceutics Reviewer
Sic Chan, PhD	Scientific Reviewer, CDRH
Gelareh Vinueza, PhD	Clinical Pharmacology Fellow
Yifei Zhang, PhD	Clinical Pharmacology Reviewer
Bilal AbuAsal, PhD	Clinical Pharmacology Team Leader
Atul Bhattaram, PhD	Pharmacometrics Team Leader
Lois Freed, PhD	Supervisory Toxicologist
David Hawver, PhD	Nonclinical Reviewer
Lana Chen, PharmD	Senior Regulatory Project Manager, Division of Regulatory Operations for Neuroscience

SPONSOR ATTENDEES

Eli Lilly and Company

Mark Mintun	VP, Pain and Neurodegeneration
Dawn Brooks	Global Brand Development Leader
John Sims	Sr. Medical Director
Christina Kiley	Sr. Director, Design Hub-Immunology Neuroscience
Elizabeth Ann Van Sant Hoffman	Sr. Director, Clinical Development
JonDavid Sparks	Research Advisor, Statistics,
Carl Garner	VP, Global Regulatory Affairs
Stephen Truocchio	Sr. Director, Global Regulatory Affairs
Angela Murff-Maxey	Advisor, Global Regulatory Affairs
Michelle Neff	Advisor, Global Regulatory Affairs, Devices
Andrew Schade	Distinguished Medical Fellow, Clinical Laboratory Sciences
(b) (4)	(b) (4)

(b) (4)

1.0 BACKGROUND

In this Type B meeting package, the sponsor is seeking the Agency's advice regarding a proposed clinical protocol that investigates donanemab as a treatment for preclinical Alzheimer's disease. The proposed protocol is I5T-MC-AACM (AACM; TRAILBLAZER-ALZ3).

Donanemab (LY3002813) is a humanized IgG1 monoclonal antibody directed specifically against an N-terminal truncated and pyroglutamate-modified Aβ peptide 3-42.

A Phase 2 randomized, double-blind, placebo-controlled, parallel-arm study I5T-MC-AACG (AACG; TRAILBLAZER-ALZ) of donanemab has been completed and a further Phase 2 randomized, double-blind, placebo-controlled, parallel-arm study I5T-MC-AACI (AACI; TRAILBLAZER-ALZ2) of donanemab is ongoing. A Phase 2 follow-on study I5T-MC-AACH (AACH; TRAILBLAZER-EXT) of donanemab is also ongoing. Studies AACG

and AACI have been conducted in patients with early symptomatic Alzheimer's disease. Other clinical studies of donanemab have also been conducted under this IND which was originally submitted on February 5, 2013.

Donanemab has been granted both Fast Track and Breakthrough Designation by the Agency.

The full protocol for Study AACM has been submitted separately to this IND on June 1, 2021.The primary objective of the study is to investigate the effect of donanemab in comparison with placebo on clinical worsening in subjects with preclinical Alzheimer's disease. (b) (4)

The proposed primary efficacy measure is the time to clinical progression as measured by the Clinical Dementia Rating Scale-Global Score (CDR-GS), (b) (4) . Many secondary efficacy measures are proposed. (b) (4)

The planned teleconference with the sponsor that has been scheduled primarily to discuss this meeting package is also to discuss several topics related to the presentation of safety data in a planned Biologics License Application (BLA) for donanemab. A separate background package dated July 2, 2021, addressing those topics, has been submitted. However, the sponsor's questions in that package are to be addressed at the planned teleconference itself, without preliminary responses to those questions being provided by the Agency.

FDA sent Preliminary Comments to Eli Lilly and Company on July 17, 2021.

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

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

(b) (4)

2.4 Additional questions in briefing package submitted on July 2, 2021

Question 9: Does FDA agree that the anticipated safety exposures in the initial BLA and the safety update to be provided during review are sufficient to review donanemab's risk/benefit profile?

FDA Preliminary Response to Question 9:
Adequate characterization of the donanemab safety profile needs to be provided at the time of the initial NDA submission. The safety data from study AACG do not provide an adequate safety database to characterize the safety of donanemab given the limited exposure and the potential to treat a large population. Blinded data from AACI (Trailblazer ALZ2) will be of limited interpretability and will not provide adequate data to characterize the safety of donanemab. Additionally, safety data from AACI that are intended to contribute to the safety database to support a marketing application need to be provided at the time of the initial NDA submission, not as a safety update.

Please provide a revised proposal for safety data that will be provided at the time of the initial NDA submission.

Meeting Discussion:
The sponsor argued that the proposed safety database may be adequate in size considering the current proposal (from the sponsor) that donanemab is to be administered to individual patients for a limited period only.

The Agency did not concur with the sponsor's argument and restated its concerns about the size of the proposed safety database. The Agency further stated that the safety database should conform as closely as possible to the International Committee on Harmonization (ICH) E1 guidance. The sponsor was also again advised to consider the feasibility of an augmentation in the size of the proposed safety database using unblinded data from Study AACI (Trailblazer ALZ2), taking into account the need to preserve the integrity of that same study.

This topic is to be further discussed, together with any new proposals by the sponsor, at the Pre-BLA meeting currently scheduled for August 26, 2021.

Question 10: Lilly intends to provide the full safety assessment of Study AACG, and comparative (nonintegrated) assessment of other donanemab safety exposures from

Phase 1 studies to characterize the safety profile and inform the risk/benefit. Does FDA agree with presentation of Phase 1 and Phase 2 data as proposed?

FDA Preliminary Response to Question 10:
It is acceptable not to pool the Phase 1 studies with the primary AACG study. However, a full safety assessment of the Phase 1 studies should be included in the submission, in addition to a comparative summary assessment.

Meeting Discussion:
None.

Question 11: Does FDA have comments on the proposed presentation of blinded safety data from ongoing studies?

FDA Preliminary Response to Question 11:
Please see the response to Question 9.

Meeting Discussion:
Please see the meeting discussion summarized under Question 9.

3.0 ADDITIONAL INFORMATION

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.[2] 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 FDA.gov.[3]

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.[4]

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 are required. Further, it describes the availability of implementation support in the form of a technical specifications document, *Study Data Technical Conformance Guide*, 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 are required in marketing application submissions for clinical and nonclinical studies that started after December 17, 2016. Standardized study data are 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.

For commercial INDs and NDAs, Standard for Exchange of Nonclinical Data (SEND) datasets are required to be submitted along with nonclinical study reports for study types that are modeled in an FDA-supported SEND Implementation Guide version. The FDA Data Standards Catalog, which can be found on the Study Data Standards Resources web page noted above, lists the supported SEND Implementation Guide versions and associated implementation dates.

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

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[2] When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

[3] https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development

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

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

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 FDA Study Data Technical 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. 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.

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 (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. 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.[6]

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

[6] https://www.fda.gov/industry/study-data-standards-resources/study-data-submission-cder-and-cber

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 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[7] and the CDER/CBER Position on Use of SI Units for Lab Tests website.[8]

[7] http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm
[8] https://www.fda.gov/media/109533/download

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*.[9]

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*.[10]

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[9] 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.
[10] https://www.fda.gov/media/85061/download

PATIENT-FOCUSED ENDPOINTS

An important component of patient-focused drug development is describing the patient's perspective of treatment benefit in labeling based on data from patient-focused outcome measures [e.g., patient-reported outcome (PRO) measures]. Therefore, early in product development, we encourage sponsors to consider incorporating well-defined and reliable patient-focused outcome measures as key efficacy endpoints in clinical trials, when appropriate, and to discuss those measures with the Agency in advance of confirmatory trials. For additional information, refer to FDA's guidance for industry *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Claims.*

NEW PROTOCOLS AND CHANGES TO PROTOCOLS

To ensure that the Division is aware of your continued drug development plans and to facilitate successful interactions with the Division, including provision of advice and timely responses to your questions, we request that the cover letter for all new phase 2 or phase 3 protocol submissions to your IND or changes to these protocols include the following information:

(1) Study phase

(2) Statement of whether the study is intended to support marketing and/or labeling changes

(3) Study objectives (e.g., dose finding)

(4) Population

(5) A brief description of the study design (e.g., placebo or active controlled)

(6) Specific concerns for which you anticipate the Division will have comments

(7) For changes to protocols only, also include the following information:

- A brief summary of the substantive change(s) to the protocol (e.g., changes to endpoint measures, dose, and/or population)
- Other significant changes
- Proposed implementation date

We recommend you consider requesting a meeting to facilitate discussion of multiple and/or complex issues.

UNITED STATES PATIENT POPULATION

FDA expects sponsors to enroll participants who are relevant to the planned use of the drug in the US population. Describe the steps you are taking to ensure that the clinical trial population will be relevant to the US patient population that will receive the drug. Include a discussion of participation of US vs. non-US sites and discuss whether the subjects likely to be enrolled will adequately represent the US patient population in terms of disease characteristics, sex, race/ethnicity, age, and standards of care. See 21 CFR 312.33(a)(2) and 21 CFR 314.50(d)(5)(v) and the guidance for industry *Collection of Race and Ethnicity Data in Clinical Trials* for more information.

We recommend you consider requesting a meeting to facilitate discussion of multiple and/or complex issues.

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 1.

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
08/19/2021 08:32:03 PM

CDER Breakthrough Therapy Designation Determination Review Template (BTDDRT)

IND/NDA/BLA #	IND 109157
Request Receipt Date	March 22, 2021
Product	Donanemab (LY3002813)
Indication	[redacted] (b) (4) ."
Drug Class/Mechanism of Action	Humanized IgG1 monoclonal antibody directed against an N-terminal pyroglutamate amyloid beta epitope
Sponsor	Eli Lilly and Company
ODE/Division	Office of Neuroscience/Division of Neurology 1
Breakthrough Therapy Request (BTDR) Goal Date (within 60 days of receipt)	May 21, 2021

Note: This document must be uploaded into CDER's electronic document archival system as a ***clinical review: REV-CLINICAL-24 (Breakthough Therapy Designation Determination) even if the review is attached to the MPC meeting minutes and*** *will serve as the official primary Clinical Review for the Breakthrough Therapy Designation Request (BTDR). Link this review to the incoming BTDR. Note: Signatory Authority is the Division Director.*

Section I: Provide the following information to determine if the BTDR can be denied without Medical Policy Council (MPC) review.

1. **Briefly describe the indication for which the product is intended (Describe clearly and concisely since the wording will be used in the designation decision letter):**

2. **Are the data supporting the BTDR from trials/IND(s) which are on Clinical Hold?** ☐YES ☒NO

3. **Was the BTDR submitted to a PIND?** ☐YES ☒NO
   If "Yes" do not review the BTDR. The sponsor must withdraw the BTDR. BTDR's cannot be submitted to a PIND.

If 2 above is checked "Yes," the BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off. If checked "No", proceed with below:

4. **Consideration of Breakthrough Therapy Criteria:**

   a. Is the condition serious/life-threatening[1])? ☒YES ☐NO

If 4a is checked "No," please provide the rationale in a brief paragraph below, and send the completed BTDDRT to Miranda Raggio for review so that the BTDR can be denied without MPC review. Once reviewed and cleared by Miranda this BTDR will be removed from the MPC calendar and you can skip to number 5 for clearance and sign-off. If checked "Yes", proceed with below:

   b. Are the clinical data used to support preliminary clinical evidence that the drug may demonstrate substantial improvement over existing therapies on 1 or more clinically significant endpoints adequate and sufficiently complete to permit a substantive review?

[1] For a definition of serious and life threatening see Guidance for Industry: "Expedited Programs for Serious Conditions—Drugs and Biologics" http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf

☒ YES, the BTDR is adequate and sufficiently complete to permit a substantive review
☐ Undetermined
☐ NO, the BTDR is inadequate and not sufficiently complete to permit a substantive review; therefore, the request must be denied because (check one or more below):

i. Only animal/nonclinical data submitted as evidence ☐
ii. Insufficient clinical data provided to evaluate the BTDR (e.g. only high-level summary of data provided, insufficient information about the protocol[s]) ☐
iii. Uncontrolled clinical trial not interpretable because endpoints are not well-defined and the natural history of the disease is not relentlessly progressive (e.g. multiple sclerosis, depression) ☐
iv. Endpoint does not assess or is not plausibly related to a serious aspect of the disease (e.g., alopecia in cancer patients, erythema chronicum migrans in Lyme disease) ☐
v. No or minimal clinically meaningful improvement as compared to available therapy[2]/ historical experience (e.g., <5% improvement in FEV1 in cystic fibrosis, best available therapy changed by recent approval) ☐

5. Provide below a brief description of the deficiencies for each box checked above in Section 4b:

If 4b is checked "No", BTDR can be denied without MPC review. Skip to number 6 for clearance and sign-off (Note: The Division always has the option of taking the request to the MPC for review if the MPC's input is desired. If this is the case, proceed with BTDR review and complete Section II). If the division feels MPC review is not required, send the completed BTDDRT to Miranda Raggio for review. Once reviewed, Miranda will notify the MPC Coordinator to remove the BTDR from the MPC calendar. If the BTDR is denied at the Division level without MPC review, the BTD Denial letter still must be cleared by Miranda Raggio, after division director and office director clearance.

If 4b is checked "Yes" or "Undetermined", proceed with BTDR review and complete Section II, as MPC review is required.

6. Clearance and Sign-Off (no MPC review)

Deny Breakthrough Therapy Designation ☐

Reviewer Signature: {See appended electronic signature page}
Team Leader Signature: {See appended electronic signature page}
Division Director Signature: {See appended electronic signature page}

Section II: If the BTDR cannot be denied without MPC review in accordance with numbers 1-3 above, or if the Division is recommending that the BTDR be granted, provide the following additional information needed by the MPC to evaluate the BTDR.

7. A brief description of the drug, the drug's mechanism of action (if known), the drug's relation to existing therapy(ies), and any relevant regulatory history. Consider the following in your response.

Alzheimer's disease is a common progressive degenerative disorder of the brain, that is both serious and life-threatening, and is currently estimated to affect more than 5 million individuals in the United States. It is now widely believed that the key pathological changes of Alzheimer's Disease (such as amyloid plaques and tau-containing neurofibrillary tangles) develop over a period of 10 to 15 years during the course of which the clinical symptoms of that condition (such as memory loss) also eventually appear; however, the pathological changes of Alzheimer's

[2] For a definition of available therapy refer to Guidance for Industry: "Expedited Programs for Serious Conditions—Drugs and Biologics" http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf

disease are widely believed to long precede the emergence of clinical symptoms. The dementia of Alzheimer's disease (also referred to as dementia of the Alzheimer's type) is itself defined as a later stage in the evolution of that disorder where cognitive deficits are sufficient to impair patients' daily functioning.

A cardinal histopathological feature of Alzheimer's disease is the presence of extracellular senile plaques in the brain containing Aβ peptides that are predominantly in a fibrillar configuration. It is hypothesized that the accumulation of Aβ peptides in the brain, resulting, in turn, from an imbalance between the production and clearance of those products, may be a significant element in the pathogenesis of that disease.

Donanemab (LY3002813) is a humanized IgG1 monoclonal antibody directed against an N-terminal pyroglutamate Aβ epitope. It is postulated that donanemab will thereby alter the pathological process underlying Alzheimer's dsease, and thus attenuate the deterioration in cognitive and functional impairment that occurs in that condition.

All fully-approved treatments for Alzheimer's disease that are currently available in the United States have been approved for the treatment of the dementia of Alzheimer's disease.

Given the wide acceptance of the view that the pathological changes of Alzheimer's disease precede the emergence of clinical symptoms, it has been proposed that if Alzheimer's disease is treated at a stage in its evolution prior to the emergence of overt dementia, especially with a product directed at attenuating that pathological process, such a treatment may be of greater benefit than one that is instituted when the disease is more advanced.

Mild cognitive impairment due to Alzheimer's disease is a term that is used for a pre-dementia stage of Alzheimer's disease that is defined by the combination of the following: impaired memory; relative preservation of other cognitive functions; absence of significantly impaired social and occupational functioning; and biomarker findings considered indicative of the Alzheimer's disease pathophysiological process. The terms "prodromal Alzheimer's disease" has also been applied to the entity that is described in the previous sentence. Under a staging system recently proposed for Alzheimer's disease under the National Institute on Aging-Alzheimer's Association (NIA-AA) criteria published in 2018, this entity will correspond approximately to Stage 4 (see Table 6 in Jack CR et al. *NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease*. Alzheimers Dement 2018; 14:535-562)

Donanemab (LY3002813) is currently under development for the indication of (b) (4) [redacted] " The category termed "early symptomatic Alzheimer's disease" by the sponsor includes patients with mild dementia due to Alzheimer's disease as well as patients with mild cognitive impairment due to Alzheimer's disease. Mild dementia due to Alzheimer's disease corresponds approximately to Stage 4 under the staging system described by Jack et al that I have cited.

There are currently no therapies fully approved for the treatment of early Alzheimer's disease, as defined by the sponsor, or for the treatment of mild Alzheimer's disease alone. However, a number of drugs have been approved for treatment of the later stages of Alzheimer's disease (see Section 8).

None of the products approved so far for the treatment of Alzheimer's disease has been demonstrated to modify the neuropathological course of Alzheimer's disease, a mechanism of action that donanemab is proposed to have.

8. Information related to endpoints used in the available clinical data:

a. Describe the endpoints considered by the sponsor as supporting the BTDR and any other endpoints the sponsor plans to use in later trials. Specify if the endpoints are primary or secondary, and if they are surrogates.

b. Describe the endpoint(s) that are accepted by the Division as clinically significant (outcome measures) for patients with the disease. Consider the following in your response:

- *A clinical endpoint that directly measures the clinical benefit of a drug (supporting traditional approval).*

The Clinical Dementia Rating Scale – Sum of Boxes (CDR-SB), a clinical endpoint, is accepted by this Division as an appropriate sole primary efficacy measure in clinical efficacy trials in a population such as that for which donanemab is to be developed for the treatment of.

- *A surrogate/established endpoint that is known to predict clinical benefit of a drug (i.e., a validated surrogate endpoint that can be used to support traditional approval).*
- *An endpoint that is reasonably likely to predict clinical benefit of a drug (supporting accelerated approval), and the endpoint used in a confirmatory trial or trials to verify the predicted clinical benefit.*

Recently, the Division determined that a reduction in brain amyloid, as measured by positron emission tomography, is reasonably likely to predict the clinical benefit of a drug in support of the accelerated approval of that drug for the treatment of Alzheimer's disease.

c. Describe any other biomarkers that the Division would consider likely to predict a clinical benefit for the proposed indication even if not yet a basis for accelerated approval.

9. A brief description of available therapies, if any, including a table of the available Rx names, endpoint(s) used to establish efficacy, the magnitude of the treatment effects (including hazard ratio, if applicable), and the specific intended population. Consider the following in your response:

There are currently no therapies approved for the treatment of early symptomatic Alzheimer's disease, as defined by the sponsor, or for the treatment of mild Alzheimer's disease only. However, three acetylcholinesterase inhibitor drugs that are currently available have been fully approved for the treatment of mild to moderate Alzheimer's disease. Those drugs and the entire spectrum of indications for which they are approved are outlined in the following table.

Drug Name	Formulation	NDA	Initial Approval Date	Mechanism of Action	Indication
Aricept® *(donepezil)*	Tablet (IR)	20690	11/1996	Acetylcholinesterase inhibitor	Mild-moderate AD (5 and 10 mg dose), Severe AD (10 mg dose)
	Oral Disintegrating Tablet (ODT)	21720	10/2004		
	23 mg tablet	22568	7/2010		Moderate-severe AD (23 mg)
Razadyne® *(galantamine)*				Acetylcholinesterase inhibitor	Mild-moderate AD
	Extended release (ER)	21615	12/2004		
Exelon® *(rivastigmine)*				Acetylcholinesterase inhibitor	Mild-moderate AD; mild-moderate PDD (since 2006) Severe AD (2013)
	Transdermal Patch	22083	7/2007 8/2012		

AD: Alzheimer's Disease; PDD: Parkinson's Disease Dementia; ODT: Orally-disintegrating tablet; IR: Immediate-release; ER: Extended-Release

Each of the three drugs listed above was initially approved for the treatment of Alzheimer's disease based on that drug having a statistically significant beneficial effect on both a cognitive co-primary efficacy measure and a global or functional co-primary efficacy measure.

Note that several of the drug formulations listed in the table above are also approved for the treatment of severe Alzheimer's disease. Namenda® (memantine), a N-methyl-D-aspartate receptor antagonist has also been approved for the treatment of moderate to severe Alzheimer's disease and is also commonly prescribed off-label for patients with mild Alzheimer's disease despite having been demonstrated not to be effective in that population. There are no other drugs approved by the FDA that to our knowledge are commonly used off-label for the treatment of overt Alzheimer's disease (i.e., dementia of the Alzheimer's type), although the acetylcholinesterase inhibitors listed in the table are commonly prescribed off-label for patients with prodromal Alzheimer's Disease (i.e., prior to the appearance of overt dementia).

None of the products that have been fully approved so far for the treatment of Alzheimer's Disease has been demonstrated to modify the pathological course of Alzheimer's Disease.

Donanemab (LY3002813) is currently under development for [redacted] (b) (4) ".

- *If the available therapies were approved under accelerated approval, provide the information for the endpoint used to support accelerated approval and the endpoint used to verify the predicted clinical benefit.*
- *In addition to drugs that have been approved by FDA for the indication, also identify those treatments that may be used off-label for that indication.*

10. A brief description of any drugs being studied for the same indication, or very similar indication, that requested breakthrough therapy designation[3].

The following table lists all drugs that have been under development for the treatment of Alzheimer's disease for which requests for Breakthrough Therapy Designation have been submitted. The proposed mechanisms of action for those drugs have also been listed.

IND #	Name of Drug	Proposed Mechanism of Action	Agency Response to Request
[redacted] (b) (4)			Denial
			Denial
			Denial
			Denial
			Denial
			Denial
			Denial
			Denial

11. Information related to the preliminary clinical evidence:

a. Table of clinical trials supporting the BTDR (only include trials which were relevant to the designation determination decision), including study ID, phase, trial design[4], trial endpoints, treatment group(s), number of subjects enrolled in support of specific breakthrough indication, hazard ratio (if applicable), and trial results.

The completed Phase 2 clinical trial of donanemab (LY3002813) whose summary results form the basis of this Breakthrough Therapy Designation request is Study I5T-MC-AACG (AACG; TRAILBLAZER-ALZ). This was a randomized, double-blind, placebo-controlled, parallel-arm study of 72 weeks duration which was conducted in 272 patients with Alzheimer's disease who met the following inclusion criteria: a gradual worsening in memory over ≥ 6 months; an entry Mini-Mental Status Examination score of 20 to 28; a positive brain florbetapir positron emission tomographic scan for amyloid; and a low-to-medium brain tau burden as demonstrated by flortaucipir positron emission tomography. These patients were randomized in equal proportions to treatment every 4 weeks with either LY3002813 at a maximum dose of 1400 mg, or placebo. The primary efficacy parameter was the change from baseline to Week 76 in the integrated Alzheimer's Disease Rating Scale (iADRS). Secondary efficacy measures included the Clinical Dementia Rating Scale – Sum of Boxes (CDR-SB), 13-item Alzheimer's Disease Assessment Scale – Cognitive (ADAS-Cog_{13}), Mini-Mental Status Examination (MMSE), and Alzheimer's Disease Cooperative Study – Instrumental Activities of Daily Living Scale (ADCS-iADL). The iARDS is a composite endpoint that combines scores on the ADAS-Cog_{13} and the ADCS-iADL, without weighting of the individual items. The iADRS has not been acceptable to this Division as a sole primary efficacy measure in clinical trials in Alzheimer's disease. A mixed model for repeated measures approach was to be used for analysis of the primary

[3] Biweekly reports of all BTDRs, including the sponsor, drug, and indication, are generated and sent to all CPMSs.
[4] Trial design information should include whether the trial is single arm or multi-arm, single dose or multi-dose, randomized or non-randomized, crossover, blinded or unblinded, active comparator or placebo, and single center or multicenter.

and secondary efficacy measures. Imaging outcomes were derived from amyloid positron emission tomography, tau positron emission tomography, and volumetric magnetic resonance imaging (MRI). Safety assessments were to include adverse events, vital signs, safety laboratory tests, vital signs, electrocardiograms, weight, safety MRI, and the Columbia-Suicide Severity Rating Scale.

The main efficacy results of Study AACG as summarized by the sponsor in this Breakthrough Therapy Designation request were as follows:

- The protocol-specified primary efficacy analysis revealed a statistically significant benefit favoring donanemab over placebo ($p = 0.042$).
- While a trend to a beneficial effect of donanemab was seen on each of the clinical secondary efficacy measures, a nominally statistically significant benefit on the change from baseline to Week 76 score was seen only for the ADAS-Cog_{13}.
- Treatment with donanemab did appear to prominently reduce amyloid plaque as compared with placebo, as measured by positron emission tomography.
- No difference between treatment groups was seen in global tau load by positron emission tomography.
- Greater reductions in whole brain volume and in regional brain volumes in selected regions of the brain were seen in the donanemab group than in the placebo group (on volumetric MRI).

The results of Study AACG, as summarized in this submission, revealed no safety concerns.

The results of Study AACG that the sponsor believes support the sponsor's view that donanemab will be a substantial improvement over current therapy (and thus support the Breakthrough Therapy Designation request) are as follows.

- A "rapid and robust" removal of Aβ plaque by donanemab compared with placebo.
- A statistically significant effect on the primary composite endpoint measuring both cognition and function and "consistent benefits across all clinically validated secondary measure of cognition and function supported by multiple statistical models."
- "Independent confirmation of underlying disease process modification shown by reductions in the progression of tau across multiple regions."

b. Include any additional relevant information. Consider the following in your response:

- *Explain whether the data provided should be considered preliminary clinical evidence of a substantial improvement over available therapies. In all cases, actual results, in addition to reported significance levels, should be shown. Describe any identified deficiencies in the trial that decrease its persuasiveness.*
- *Identify any other factors regarding the clinical development program that were taken into consideration when evaluating the preliminary clinical evidence, such as trial conduct, troublesome and advantageous aspects of the design, missing data, any relevant nonclinical data, etc.*
- *Safety data: Provide a brief explanation of the drug's safety profile, elaborating if it affects the Division's recommendation.*

12. Division's recommendation and rationale (pre-MPC review):

☒ GRANT:

Provide brief summary of rationale for granting:

Alzheimer's disease is a serious disease for which the current fully-approved treatment options are limited. Moreover, the current fully-approved treatment options for Alzheimer's disease are believed to result in those limited benefits through mechanisms other than by modifying the pathological course of Alzheimer's disease.

On the other hand, the hypothesized mechanism of action of donanemab in Alzheimer's disease, as already described, is through binding to an Aβ epitope, leading to a reduction in brain amyloid, and thus beneficially influencing the pathological course of Alzheimer's disease. Thus, donanemab has a postulated mechanism of action that is different from that of the drugs currently fully-approved for the treatment of Alzheimer's disease and has the potential for addressing an unmet medical need.

The summary results of the Phase 2 study, I5T-MC-AACG (AACG; TRAILBLAZER-ALZ), as provided by the sponsor do not in form provide clear evidence of the efficacy of donanemab on a clinical efficacy measure. Although, a statistically significant treatment difference favored donanemab over placebo has been reported on the primary efficacy measure, the Instrumental Activities of Daily Living scale (iADRS), that instrument, as already noted, has not been acceptable to this Division as a sole primary efficacy measure in clinical trials in Alzheimer's disease. At the same time, the summary results of Study AACG appear to indicate that treatment with donanemab has led to a reduction in brain amyloid on positron emission tomography as compared with placebo.

As already noted, the Division has recently determined that a reduction in brain amyloid, as measured by positron emission tomography, is reasonably likely to predict the clinical benefit of a drug in support of the accelerated approval of that drug for the treatment of Alzheimer's disease. Thus, the reported effects of donanemab on brain amyloid in Study AACG, that are currently available, are sufficient to support the grant of this Breakthrough Therapy Designation request for donanemab in the treatment of Alzheimer's disease.

Note, if the substantial improvement is not obvious, or is based on surrogate/pharmacodynamic endpoint data rather than clinical data, explain further.

☐ DENY:

Provide brief summary of rationale for denial:

Note that not looking as promising as other IND drugs is not a reason for denial; the relevant comparison is with available (generally FDA-approved) therapy. If the Division does not accept the biomarker/endpoint used as a basis for traditional approval or accelerated approval or as a basis for providing early clinical evidence of a substantial improvement over available therapy, explain why:

13. Division's next steps and sponsor's plan for future development:

A further clinical efficacy study of donanemab similar in design to Study AACG is ongoing. This ongoing protocol is Study I5T-MC-AACI (AACI; TRAILBLAZER-ALZ2). This is also a randomized, double-blind, placebo-controlled, parallel-arm study of 72 weeks duration; it is being conducted in about 500 patients with Alzheimer's disease who meet the following inclusion criteria: a gradual worsening in memory over ≥ 6 months; an entry Mini-Mental Status Examination score of 20 to 28; a positive brain florbetapir positron emission tomographic scan for amyloid; and a low-to-high brain tau burden, as demonstrated by flortaucipir positron emission tomography. These patients are being randomized in equal proportions to treatment every 4 weeks with either donanemab at a maximum dose of 1400 mg, or placebo. The primary efficacy parameter is the change from baseline to Week 76 in the CDR-SB. Secondary efficacy measures include the iADRS, ADCS-iADL, ADAS-Cog_{13}, and MMSE. A mixed model for repeated measures approach is to be used for analysis of the primary and secondary efficacy measures. Imaging outcomes are to be derived from amyloid positron emission tomography, tau positron emission tomography, and volumetric magnetic resonance imaging (MRI). Safety assessments are to include

adverse events, vital signs, safety laboratory tests, vital signs, electrocardiograms, weight, safety MRI, and the Columbia-Suicide Severity Rating Scale. Plasma concentrations of donanemab are to be measured, as are the concentrations of treatment-emergent neutralizing antibodies. The design of this study has previously been discussed with the Agency.

a. If recommendation is to grant the request, explain next steps and how the Division would advise the sponsor (for example, plans for phase 3, considerations for manufacturing and companion diagnostics, considerations for accelerated approval, recommending expanded access program):

b. If recommendation is to deny the request and the treatment looks promising, explain how the Division would advise the sponsor regarding subsequent development, including what would be needed for the Division to reconsider a breakthrough therapy designation:

14. List references, if any:

15. Is the Division requesting a virtual MPC meeting via email in lieu of a face-to-face meeting? YES ☒ NO ☐

16. Clearance and Sign-Off (after MPC review):

Grant Breakthrough Therapy Designation ☒
Deny Breakthrough Therapy Designation ☐

Reviewer Signature: {See appended electronic signature page}
Team Leader Signature: {See appended electronic signature page}
Division Director Signature: {See appended electronic signature page}

Revised 10/13/20 /M. Raggio

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/

RANJIT B MANI
06/21/2021 05:03:31 PM

TERESA J BURACCHIO
06/21/2021 08:18:56 PM