CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761269Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 105081

MEETING MINUTES

Eisai Inc.
Attention: Stacie P. O'Sullivan
Global Regulatory Strategy
155 Tice Boulevard
Woodcliff Lake, NJ 07677

Dear Ms. O'Sullivan:[1]

Please refer to your Investigational New Drug Application (IND) submitted under Section 505(i) of the Federal Food, Drug, and Cosmetic Act for lecanemab (BAN 2401).

We also refer to the meeting (teleconference) between representatives of your firm and the FDA on September 10, 2021. The purpose of the meeting was to discuss the development plan for lecanemab.

A copy of the official minutes of the meeting (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: Guidance

Meeting Date and Time: September 10, 2021, from 10:00 AM to 12:00 PM ET
Meeting Location: By Teleconference

Application Number: IND 105081
Product Name: Lecanemab (BAN2401)
Indication: Alzheimer's disease
Sponsor Name: Eisai, Inc.
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

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
Brian Trummer, MD, PhD	Clinical Reviewer, DN1
Sally Jo Yasuda, PharmD, MS	Clinical Safety Team Leader

Division of Regulatory Operations for Neuroscience

E. Andrew Papanastasiou, MS, PharmD	Senior Regulatory Project Manager, Division of Regulatory Operations for Neuroscience

Division of Pharmacology/Toxicology for Neuroscience

Lois Freed, PhD	Supervisory Toxicologist
Christopher Toscano, PhD	Nonclinical Reviewer

Office of Scientific Investigations

Cara Alfaro, PharmD	Clinical Analyst, Office of Scientific Investigations (OSI)

Office of Translational Sciences

Kun Jin, PhD	Biostatistics Team Leader
Hsien Ming Hung, PhD	Director, Division of Biometrics I
Tristan Massie, PhD	Biostatistical Reviewer
Michael Bewernitz, PhD	Pharmacometrics Reviewer
Xiaohan Cai, PhD	Clinical Pharmacology Reviewer
Bilal AbuAsal, PhD	Clinical Pharmacology Team Leader

Office of Product Quality

Haoheng Yan, PhD	Biopharmaceutics Team Leader
Gunter Boekhoudt, PhD	Biopharmaceutics Reviewer
Maxwell Van Tassel, PhD	Microbiology Reviewer

Office of Surveillance and Epidemiology

Karen Long, PharmD	Safety Evaluator, Division of Pharmacovigilance I
Charlene Flowers, RPh	Safety Evaluator, DPVI
David Croteau, MD	Medical Officer, DPVI
Jacqueline Sheppard, PharmD	Risk Management Analyst, Division of Risk Management (DRM)
Lindsey Crist, PharmD, BCPS	Reviewer, DRM
Kira Leishear, PhD	Lead Epidemiologist, Division of Epidemiology I (DEPII)
Dinci Pennap, PhD	Epidemiologist, DEPII
Sukhminder Sandhu	Deputy Director, DEPII
Wei Hua	Associate Director, DEPII
Darrel Jenkins, MS	Supervisory Regulatory Health Project Manager

SPONSOR ATTENDEES

Lynn Kramer, MD, FAAN	Chief Clinical Officer, Neurology Business Group (NBG)	Eisai
Melissa Campo	Director, CMC Coordination	Eisai
Shobha Dhadda, PhD	Vice President, Biostatistics and Clinical Development Operations, NBG	Eisai
Wolfgang Ebel	Director, CMC Program Management	Eisai
Amanda Goodwin	Executive Director, Global Regulatory Strategy, NBG	Eisai
Mark Hodgkinson	Associate Director, Global Regulatory Strategy, NBG	Eisai
Ziad Hussein, PhD	Executive Director, Head, Modelling and Simulation	Eisai
Michael Irizarry, MD	Vice President, Clinical Research, NBG	Eisai
Lisa Kahn (MT) ASCP	Director, CMC Regulatory Affairs	Eisai
Michio Kanekiyo, MS	Director, Biostatistics, NBG	Eisai
Akihiko Koyama, PhD	Executive Director, Global Head Translational Science, NBG	Eisai
Ishani Landry, PhD	Senior Director, Clinical Pharmacology, NBG	Eisai
David Li, PhD	Senior Director, Biostatistics, NBG	Eisai
Stacie O'Sullivan	Director, Global Regulatory Strategy, NBG	Eisai

Stuart Pullen, PhD	Director, CMC Regulatory Affairs	Eisai
Larisa Reyderman, PhD	Vice President, Clinical Pharmacology and Translational Medicine, NBG	Eisai
Chad Swanson, PhD	Executive Director, Clinical Research, NBG	Eisai
Andrew Taylor, DPhil (Oxon)	Associate Director, CMC Regulatory Affairs	Eisai
Thomas Visalli, PhD, DABT	Senior Director, Nonclinical Regulatory Affairs	Eisai
Jaren Landen, PhD	Early Alzheimer's Disease Head, Neurodegenerative DU	Biogen
John Ruesch, MBA	Head of Protein Development	Biogen

1.0 BACKGROUND

In this Type B meeting package, the sponsor seeks the Agency's advice regarding the further development of lecanemab (BAN2401) for the treatment of Alzheimer's disease, specifically the contents of a Biologics License Application (BLA) for this product.

Lecanemab is a humanized IgG1 monoclonal antibody directed against soluble Aβ protofibrils. The lecanemab drug product is administered intravenously.

A Breakthrough Therapy Designation request for lecanemab for the treatment of Alzheimer's disease was granted by the Agency in a letter dated June 21, 2021.

Three clinical studies of lecanemab have been completed and are summarized in this meeting package. These include Study BAN2401-GOO1-201 Core (Study 201 Core), a Phase 2 randomized, double-blind, placebo-controlled, parallel-arm study of 18 months' duration conducted in patients with mild cognitive impairment due to Alzheimer's disease and mild dementia due to Alzheimer's disease (this study had a Bayesian adaptive design). Multiple lecanemab biweekly and monthly dosing regimens were compared with placebo, in parallel, in that study. The primary efficacy measure for this study was the Alzheimer's Disease Composite Score (ADCOMS), with the Clinical Dementia Rating Scale – Sum of Boxes (CDR-SB) and Alzheimer's Disease Assessment Scale – Cognitive (ADAS-Cog) being key clinical secondary efficacy measures. A measure derived from brain amyloid positron emission tomography was also a key secondary efficacy measure in that study.

An open-label extension to Study 201 Core (Study 201 OLE; Study 201 OLE Phase) is currently ongoing. Also ongoing are the following: Study BAN2401-G000-301 Core (Study 301 CORE; CLARITY AD), a randomized, double-blind, placebo-controlled, parallel-arm study of 18 months' duration in patients with mild cognitive impairment due to Alzheimer's disease or mild dementia due to Alzheimer's disease that compares lecanemab in a dose of 10 mg/kg biweekly with placebo, and uses the CDR-SB as the primary efficacy measure; Study 301 OLE (an open-label extension to Study 301 Core); and Study BAN2401-G000-303 Core (Study 303), a randomized, double-blind, placebo-controlled, parallel-arm study of lecanemab in preclinical Alzheimer's disease.

In the initial BLA for lecanemab, the sponsor proposes to seek approval of lecanemab under the accelerated approval regulations. The efficacy data in support of that initial application, which will be derived from Study 201 Core and Study 201 OLE, are to primarily provide evidence that lecanemab (a monoclonal antibody directed at aggregated beta amyloid) reduces brain amyloid on positron emission tomography, an effect that the Agency has determined to be reasonably likely to predict clinical benefit in Alzheimer's disease. The efficacy data for Study 201 Core and Study 201 OLE are summarized in this meeting package.

The results of Study 301 are to later provide (confirmatory) evidence of the clinical benefit of lecanemab, as required under the accelerated approval regulations, assuming that lecanemab is first granted accelerated approval as described above.

Other topics covered in this meeting package include, but are not limited to, the following, all of which are regarding the proposed BLA for lecanemab: available observed safety data from Study 201 Core and Study 201 OLE; the content of the safety data to be provided with the initial BLA and 120-day safety update; pharmacokinetic data, including analyses, to be submitted with the initial BLA; a possible rolling BLA for lecanemab; nonclinical data; and other items. These are each described in more detail in the meeting package.

FDA sent Preliminary Comments to Eisai on September 8, 2021.

2.0 DISCUSSION

Question 1: Reduction in cerebral amyloid beta (Aβ) plaque has been established as a surrogate endpoint considered reasonably likely to predict clinical benefit (reduction in clinical decline) in subjects with early AD. Biomarker results from Study 201 Core and OLE Phase show an effect of lecanemab on target engagement (brain Aβ plaque reduction by amyloid PET, increase in CSF Aβ1-42 levels, and increase in plasma Aβ 42/40 levels). Based on these biomarker results, which correlate to clinical outcomes in Study 201 Core, Eisai proposes to submit the BLA for lecanemab via the Accelerated Approval pathway. Does the Division have feedback on this proposal?

FDA Response to Question 1:
Please see the response to Question 5.

Discussion:
None.

Question 2: Confirmatory trial(s) to verify clinical benefit are required for products approved under the Accelerated Approval pathway. Eisai proposes to submit the results of Study 301 Core, when completed, as the confirmatory clinical trial to verify the clinical benefit of lecanemab. Does the Division have feedback on this proposal?

FDA Response to Question 2:
This proposal is acceptable, in concept.

Discussion:
None.

Question 3: Given the status of the lecanemab development program, Eisai proposes to submit the BLA for Accelerated Approval via Rolling Review. Does the FDA have feedback on this proposal?

FDA Response to Question 3:
In general, a rolling submission will be acceptable for lecanemab, as it has Breakthrough Therapy Designation; however, please refer to the responses to Questions 4 and 22 regarding specific concerns with the timeline that you have proposed for the rolling submission.

You will need to submit, to this IND, a formal request and proposed schedule for submission of portions of your proposed BLA for lecanemab. We refer you to Appendix 2 headed "*Processes for Rolling Review*" in the Guidance for Industry entitled "*Expedited Programs for Serious Conditions – Drugs and Biologics*".[2]

Discussion:
None.

Question 4: If the FDA agrees to a BLA submission for Accelerated Approval via Rolling Review for lecanemab:

a) Eisai proposes to submit portions of the BLA as outlined in Table 21: complete nonclinical (Oct 2021), complete clinical (Dec 2021) and CMC (Dec 2021, Apr 2022, Jun 2022).

b) Eisai requests consideration that the BLA submission via rolling review be granted Priority Review designation.

c) Eisai requests consideration that the (1) Filing Review and, (2) Priority Review PDUFA clock begin 31 Dec 2021 (i.e.. 8 months, resulting in a target approval of 31 Aug 2022) given that at this time the FDA will have complete nonclinical, clinical and partial CMC Modules.

d) Eisai proposes that if there is pre-agreement with the FDA on the CMC submission timing and content via Rolling Review, that this approach would not constitute a Major Amendment per MAPP 6010.8 Rev. 1.

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

Does the FDA have any feedback on these proposals?

FDA Response to Question 4:
Responses to your proposals described under Parts a, b, c, and d of this question are provided below.

a) This proposal is not acceptable. Please see our responses to Question 4c and Question 22.

b) A request for priority review of your application will be considered at the time of filing of your planned BLA for lecanemab.

c) No, we are unable to agree with your proposed timeline regarding the start of the Prescription Drug User Fee Act (PDUFA) clock. The submission of a complete Chemistry, Manufacturing, and Controls (CMC) module is necessary for starting the PDUFA clock. Please also see our response to Question 22.

d) Please see our response to Question 22.

Discussion:
None.

Question 5: The BLA for lecanemab under the Accelerated Approval pathway will be supported by biomarker and efficacy data from the following study:

- BAN2401-G000-201 Core and 201 OLE Phase: A Placebo-Controlled, Double-Blind, Parallel-Group, Bayesian Adaptive Randomization Design and Dose Regimen-finding Study with an Open-Label Extension Phase to Evaluate Safety, Tolerability and Efficacy of BAN2401 in Subjects with Early Alzheimer's Disease.

Does the Division agree?

FDA Response to Question 5:
The proposed efficacy and biomarker data from BAN2401-G000-201 Core and BAN2401-G000-201 OLE appear sufficient, in form, to support the submission of a marketing application for lecanemab.

Discussion:
None.

Question 6: The BLA for lecanemab under the Accelerated Approval pathway will be supported by safety data from the following studies:

- BAN2401-A001-101: A Randomized, Double-blind, Placebo-controlled, Combined Single Ascending Dose and Multiple Ascending Dose Study to Assess Safety, Tolerability, Immunogenicity, Pharmacodynamic Response, and Pharmacokinetics of Intravenous Infusions of BAN2401 in Subjects with Mild to Moderate Alzheimer's disease

- BAN2401-J081-104: A Randomized, Double-Blind, Placebo-Controlled Study to Assess Safety, Tolerability, Pharmacokinetics, Immunogenicity, and Pharmacodynamic Response of Repeated Intravenous Infusions of BAN2401 in Subjects with Mild Cognitive Impairment due to Alzheimer's Disease and Mild Alzheimer's Disease

- BAN2401-G000-201: A Placebo-Controlled, Double-Blind, Parallel-Group, Bayesian Adaptive Randomization Design and Dose Regimen-finding Study with an Open-Label Extension Phase to Evaluate Safety, Tolerability and Efficacy of BAN2401 in Subjects with Early Alzheimer's Disease

- BAN2401-G000-201 OLE: Open Label Extension Phase to BAN2401-G000-201

- Blinded safety data from Study BAN2401-G000-301: A Placebo-Controlled, Double-Blind, Parallel Group, 18-Month Study With an Open-Label Extension Phase to Confirm Safety and Efficacy of BAN2401 in Subjects with Early Alzheimer's Disease

- BAN2401-G000-301 OLE: Open Label Extension Phase to BAN2401-G000-301 (blinded as to treatment assignment in Study 301 Core)
- Blinded safety data from Study BAN2401-G000-303 AHEAD 3-45: A Placebo-Controlled, Double-Blind, Parallel-Treatment Arm, 216 Week Study to Evaluate Efficacy and Safety of Treatment with BAN2401 in Subjects with Preclinical Alzheimer's Disease and Elevated Amyloid (A45 Trial) and in Subjects with Early Preclinical Alzheimer's Disease and Intermediate Amyloid (A3 Trial)

- BAN2401-A001-004: An Open-Label, Parallel-Group, Randomized Study to Evaluate the Absolute Bioavailability of Single Dose Subcutaneous Administration of Lecanemab in Healthy Subjects (only safety data provided in the 120-Day Safety Update, with no CSR submission proposed)

Does the Division agree that the proposed safety database supports submission of the BLA?

FDA Response to Question 6:

On face, the proposed safety database appears sufficient to support the submission of a marketing application for lecanemab.

Discussion:
None.

Question 7: Eisai proposes to provide synoptic CSRs for ongoing Studies 301 Core, 301 OLE Phase, and 303 to describe the safety of lecanemab. Eisai proposes the following for the 3 synoptic CSRs:

- Section 2 – Methodologies and summary of blinded deaths and Serious Adverse Events (SAEs)
- Appendix 16.1.1 – protocol and amendments
- Appendix 16.2.7 – blinded deaths and SAE Listings that do not include ARIA-E, ARIA-H, skin rash and other hypersensitivity reactions (including infusion reaction events)
- Subject narratives and case report forms (CRFs) will not be provided

Does the Division agree?

FDA Response to Question 7:
We do not agree with your proposal. Regarding Appendix 16.2.7, we request that the BLA includes blinded listings from Studies 301 Core, 301 OLE, and 303 for deaths, discontinuations due to adverse events, and serious adverse events related to ARIA-E, ARIA-H, skin rash, and other hypersensitivity reactions. We also request that you include the subject narratives and case report forms for these events. We are open to a discussion at the meeting regarding how these blinded data can be submitted to the BLA.

Discussion:
The sponsor acknowledged the Agency's request for blinded listings for deaths, discontinuations to adverse events, and serious adverse events. The submission should include all SAEs, including those related to ARIA-E, ARIA-H, skin rash, and other hypersensitivity reactions, together with subject narratives and case report forms for those events.

The mechanism by which the above data are to be provided to the Agency was further discussed at the meeting. The Agency stated that the requested data should be provided to the Agency by an appropriately firewalled team. The Agency also emphasized that it would be important, when submitting the requested data, for the integrity of the study not to be violated. The requested data should be submitted to the Division and not to the FDA Adverse Event Reporting System (FAERS).

The Agency confirmed that statistical datasets would not need to be provided for the above events.

The sponsor is to provide proposals for addressing the above.

Question 8: The clinical module proposed for submission mid-December 2021 will present all lecanemab data as of 30 Jun 2021. Does the Division agree with the proposed data cut date?

FDA Response to Question 8:
The proposed data cut date appears acceptable.

Discussion:
None.

Question 9: Eisai proposes to submit the 120-Day safety during Apr 2022. The update will be based on data obtained through 31 Dec 2021. Does the Division agree?

FDA Response to Question 9:
Your proposal for the 120-day safety update appears acceptable. The safety update should include updated safety datasets for Studies 201 Core and 201 OLE, as applicable, as well as updated immunogenicity datasets and an updated immunogenicity summary. Please also see our response to Question 7.

Discussion:
None.

Question 10: Does the FDA agree with submitting PK data for the Drug Product manufactured under Process (b) (4) on the following rolling submission schedule?

- Process (b) (4): Study 201 Core: as part of clinical module submission (15 Dec 2021)
- Process (b) (4): Study 201 OLE: as part of clinical module submission (15 Dec 2021)
- Process (b) (4) (Clinical Formulation): Study 004: as part of the 120-Day Safety Update

FDA Response to Question 10:
Your proposed timeline appears acceptable. However, the reliability of pharmacokinetic comparability to establish a bridge across manufacturing processes will depend on the adequacy of CMC comparability. If pharmacokinetic comparability is needed to establish the bridge, you should provide more details about the adequacy of pharmacokinetic sampling, and the rationale for the proposed criteria for pharmacokinetic comparability in future submissions.

Discussion:
None.

Question 11: Does the FDA agree with PK and Exposure-Response analysis completed based on Study 201 Core for the BLA submission as listed below:

- Population PK analysis
- PK/PD analysis correlating exposure with amyloid PET SUVr
- PK/PD analysis correlating PET SUVr with key clinical endpoints (ADCOMS, CDRSB, ADAS-Cog)
- PK/PD analysis correlating exposure with key clinical endpoints (ADCOMS, CDR-SB, ADAS-Cog) and the exploratory endpoint MMSE
- PK/PD analysis correlating exposure with CSF biomarkers including Aβ42, Neurogranin, NFL, YKL-40, Contactin2
- Exposure-safety analysis correlating exposure with ARIA-E

FDA Response to Question 11:

You indicate that anti-drug antibody (ADA) status is not a significant covariate for clearance in the population pharmacokinetic model. However, it is not clear that you have addressed the effect of time-varying assessments of immunogenicity on pharmacokinetics in your analyses. You should assess the relationship of the time-varying ADA status, ADA titer, neutralizing antibody (NAb) status, and NAb titer on pharmacokinetic assessments as well as relevant pharmacodynamic, efficacy, and safety assessments. You may also consider stratifying clinical outcomes and biomarker measurements by early ADA appearance or late ADA appearance. For example, subjects who 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 analysis may help explain the findings in this study, taking into consideration the time-varying nature of the formation of ADA and their role in increasing clearance of lecanemab.

You also indicate that the E_{max} for positron emission tomographic standard uptake value ratio (SUVr) was unaffected by neutralizing ADA. However, it is not clear that the effect of immunogenicity was assessed on parameters other than the E_{max} (i.e., K_{in}, EC_{50}). Your covariate searches should assess the effect of immunogenicity on key structural model parameters, particularly those for pharmacodynamics, efficacy, and safety. Please note that the determination of whether an immunogenicity assessment is a significant covariate in a model is, in and of itself, of limited value as that determination is sensitive to sample size and selection of alpha, and does not inform the effect size. You should address the effect size of immunogenicity on pharmacokinetics, pharmacodynamics, efficacy, and safety.

You stated that drug interference in ADA and NAb testing may impact the classification of ADA and NAb in some patients in Study 201. You need to clarify the impact of such a phenomenon on pharmacokinetics, pharmacodynamics, efficacy, and safety. Similarly, you need to clarify whether a high titer of ADA may have an impact on the validity of the pharmacokinetic assay for lecanemab.

Discussion:
To ensure alignment on the proposed analyses for immunogenicity, the sponsor proposed to submit a draft Integrated Summary of Immunogenicity (ISI) analysis plan to the Agency by the end of September 2021 and then meet with the Agency to provide an overview of the plan and answer any questions that the Agency might have. The Agency concurred with the sponsor's plan to submit the draft ISI, and recommended that that submission be accompanied by a request for comments and advice. If, based on the Agency's response, the sponsor then concludes that a meeting with the Agency is needed, a meeting request should then be submitted.

Question 12: Eisai proposes to provide:

- The narrative portion of the ISE report in Module 2 as the SCE, and
- The narrative portion of the ISS report in Module 2 as the SCS

Does the FDA agree?

FDA Response to Question 12:
Your proposals for the Integrated Summary of Efficacy (ISE) and the Integrated Summary of Safety (ISE) reports are acceptable.

Discussion:
None.

Question 13: The ISE report will contain a summary of biomarker, ER and efficacy data from Study 201 Core and OLE Phase. No pooling is proposed. Does the FDA agree with this proposal?

FDA Response to Question 13:
Your approach is acceptable.

Discussion:
None.

Question 14: The ISS for lecanemab will be an integrated presentation and discussion of individual study data (completed and ongoing), with no pooling proposed. Does the FDA agree with this proposal?

FDA Response to Question 14:
The proposal for the ISS is acceptable. We request that, if Study 201 Core and Study 201 OLE data are contained in the same Adverse Event Analysis Dataset (ADAE), a flag be included to define the data from the two study phases.

Discussion:
None.

Question 15: In accordance with FDA Specifications for Preparing and Submitting Summary Level Clinical Site Data for the Center for Drug Evaluation and Research's (CDER's) Inspection Planning, Eisai proposes to construct the dataset based on the Study 201 Core and OLE Phase. Does the FDA agree?

FDA Response to Question 15:
We agree with your proposal.

Discussion:
None.

Question 16: For all studies, Eisai proposes to submit study-level data in electronic Common Technical Document (eCTD) format in Module 5.3.5.1. Eisai will also submit:

- Statistical Analysis System (SAS) programs to create all Analysis Data Model (ADaM) datasets for Phase 2 Study 201
- SAS programs for creating key safety tables and figures
- SAS programs to create the tables and figures for all primary and key secondary efficacy analyses for the Study 201

All other data and program files will be provided to the FDA upon request. Does the FDA agree?

FDA Response to Question 16:
Your proposal is acceptable.

Discussion:
None.

Question 17: For all ISS data, Eisai does not intend to update the MedDRA coding at the study level datasets for adverse events. The coding updates will be implemented in the ISS ADaM datasets only. Does the FDA agree?

FDA Response to Question 17:
Your proposal is acceptable.

Discussion:
None.

Question 18: For all studies, Eisai requests a waiver on Appendix 16.4 Individual Data Listing, in the study-level CSR. The pertinent subject data listings will be presented in Appendix 16.2 Selected Patient Data Listing, in the CSR. Does the FDA agree?

FDA Response to Question 18:
Your proposal is acceptable.

Discussion:
None.

Question 19: Eisai proposes to include a list of all subject narratives in the ISS report. This list will directly hyperlink to the location of previously-created patient narratives in individual CSRs as well as any narratives that are newly created for the ISS report. Does the FDA agree with this proposal?

FDA Response to Question 19:
We do not agree with your proposal. For ease of review, we ask that all subject narratives in the ISS be submitted in a single portable document format (PDF) file.

Discussion:
None.

Question 20: Guidance for Industry Premarketing Risk Assessment (2005) suggests that "Case report forms (CRFs) submitted for subjects who died or discontinued a study prematurely due to an adverse event should include copies of relevant hospital records, autopsy reports, biopsy reports, and radiological reports, when feasible". Eisai proposes to provide this level of documentation and Council for International Organizations of Medical Sciences (CIOMS I) forms only for those subjects who died where the death was related to study drug. Does the FDA agree?

FDA Response to Question 20:
We do not agree with your proposal. This level of documentation and CIOMS forms should be provided for all subjects who died or discontinued a study prematurely due to an adverse event, regardless of assessed causality. Please also see our response to Question 7.

Discussion:
None.

Question 21: Does the FDA agree that the completed nonclinical evaluation of lecanemab is sufficient to support review of a BLA?

FDA Response to Question 21:
As we have previously stated (in meeting minutes issued on December 6, 2012, and November 8, 2018, for meetings held on November 6, 2012, and October 9, 2018, respectively) the available nonclinical studies are sufficient to support submission of a BLA for lecanemab. However, you will need to provide data to demonstrate comparability between the drug material(s) used for the pivotal nonclinical studies and the commercial product. Please also see our response to Question 22.

The adequacy of the nonclinical studies will be a matter of review at the time of BLA submission.

Discussion:
None.

Question 22: As outlined in Questions 3 and 4, a Rolling BLA Review is proposed. As part of this Rolling Review, Eisai proposes to submit partial CMC leafs (Table 24), so that information can be provided as it becomes available.

a) Does the FDA agree with Eisai's proposal to submit partial CMC leafs (Table 24)?

b) Does the FDA agree Eisai's proposed submission schedule (Table 24)?

c) Updates to partial leaf submissions will clearly identify new information to support a streamlined review. Operationally, does the FDA have any preferences regarding how updates to partial leaves will be identified?

FDA Response to Question 22:
Responses to your proposals described under Parts a, b, and c of this question are provided below.

a) No, we do not agree with the proposed CMC submission plan described in Table 24. A complete CMC module is necessary for starting the PDUFA clock. The CMC module is not considered complete until all the CMC information is submitted (currently proposed for June 2022, according to Table 24). We have the following additional comments regarding the expected CMC data for your proposed BLA:

   i. Eisai is expected to manufacture at least one drug substance (DS) and drug product (DP) batch at each manufacturing site during the review cycle for inspection purposes.

   ii. The clinical efficacy data to be included in your initial BLA submission are to be from Studies 201 and 201 OLE, which used Process (b) (4) and (b) (4) materials, while future confirmatory clinical studies will use Process (b) (4) material. Therefore, all these process changes are late-stage changes. Per ICH Q5E, comprehensive and thorough analytical comparability exercises are expected for Processes (b) (4) materials (for drug substance and drug product).

   iii. We are not clear which DS material (b) (4) will be used for DP process performance qualification (PPQ) runs. If clinical DS material is

used for DP PPQ runs, please note that process and release data for DP manufactured from commercial process DS are expected as part of the complete BLA submission.

b) Please refer to our response to Question 22a above.

c) Please refer to our response to Question 22a above.
Please also see our additional comments in the section "ADDITIONAL INFORMATION" regarding the preparation of the CMC leaves of your proposed application.

Discussion:
Several components of Question 22 were each discussed further as outlined below.

Question 22a:
The sponsor's plans for a rolling submission of Module 3 were presented in a series of slides; the sponsor stated that those plans were intended to facilitate an efficient review. The sponsor's plans were then discussed further.

The sponsor acknowledged that the PDUFA clock would not start until the complete Module 3 had been submitted to the Agency for review. The Agency stated that since lecanemab had received breakthrough therapy designation, the Agency could exercise a degree of flexibility, such as accepting a division of Module 3 into complete DS and DP sections for a rolling submission. However, the sponsor's proposal for submitting Module 3 under a rolling submission, as presented in Slides 4 and 5 for the DS and DP, respectively, would not facilitate the review of Module 3. From the Agency's perspective, the sections to be included in the sponsor's proposed second wave for both DS and DP are critical items of information that are usually reviewed early in the review cycle, since the outcome of their review could impact the review of other components of Module 3. For that reason, the Agency believed that the review of a single, well-organized, and complete Module 3 submission would be more efficient. Alternatively, the Agency would be willing to accept a rolling submission of Module 3 under which the DS and DP sections would each be provided in their entirety rather than in two waves. Simple stability data updates could then be submitted during the course of the review cycle.

The sponsor acknowledged the Agency's views regarding the submission of Module 3, as described above, and is to consider the possibility of submitting the DS and DP sections in their entirety under a rolling submission.

Question 22aii:
The sponsor agreed to provide the results of all three comparability studies (comparability of Process (b) (4) in a single comparability package.

The Agency stated that the sponsor's stepwise approach to demonstrate comparability between Processes (b) (4) appeared reasonable. The Agency acknowledged the comparability amendments that had been submitted to IND 105081. The Agency then pointed out that review of the March 2019 comparability data between Process (b) (4) and (b) (4) was performed based on the understanding that the Process (b) (4) change was an early-stage change. However, the Process (b) (4) change is now considered a late-stage change. In fact, the following changes between processes are all considered late-stage changes: (b) (4) Thus, the expectation, per ICH, is that the comparability exercise should be comprehensive and thorough. The Agency recommended that the sponsor conduct a review of the comparability data generated to determine whether all the comparability results met the expectation for late-stage change.

To facilitate the review of the comparability data in the BLA, the Agency suggested that the sponsor provide the comparability data for Processes (b) (4) side-by-side in a table. The Agency further clarified that the side-by-side comparison requested was a summary of existing data and a further study of the comparability of Processes (b) (4) was not being requested, unless the sponsor later was of the view that such a study was needed.

The sponsor proposed submitting the protocol investigating the comparability of Process (b) (4) to Process (b) (4) for the Agency to review, followed by an *ad hoc* teleconference to reach agreement with the Agency regarding the design of that comparability study. The Agency agreed with that proposal and urged the sponsor to submit a formal meeting request for that teleconference at the same time as the comparability protocol.

Question 22ai:
The sponsor acknowledged the Agency's expectation that DS and DP manufacture would occur during the review cycle.

Question 22aiii:
The sponsor confirmed that DP PPQ manufacturing will be conducted using DS material manufactured using Process (b) (4).

Question 23: Provided that analytical comparability of Process (b) (4) to Process (b) (4) is demonstrated, Eisai proposes to claim commercial shelf life for drug substance and drug product based on real time drug substance and drug product stability data obtained from material manufactured according to Process (b) (4) The proposed approach and temporal availability of stability data is outlined below. Does the FDA agree, subject to evaluation of all data?

FDA Response to Question 23:
Your proposal to claim commercial shelf life for DS and DP based on real time DS and DP stability data obtained from material manufactured according to Process

(b) (4) appears reasonable, pending review of the comparison of processes and the demonstration of comparability between Process (b) (4) and Process (b) (4) The determination of expiry is a review issue.

Discussion:
None.

Question 24: Eisai proposes (b) (4) months shelf life for drug product to support cold chain logistics, with 6 months real time drug product data submitted to the FDA in Jun 2022. Does the FDA agree with this proposal?

FDA Response to Question 24:
Please refer to our response to Question 23 regarding setting shelf-life. You may extend commercial DS and DP shelf-life based on stability data obtained from studies conducted according to post-approval stability study protocols, which will be reviewed as part of the proposed BLA for lecanemab. Assuming all data meet stability specifications, you may submit information regarding shelf-life extensions via BLA annual reports.

Discussion:
None.

Question 25: In accordance with the 21 CFR 54, Eisai plans to include financial certification for all applicable investigators from the adequate and well-controlled Phase 2 Studies 201 Core and 201 OLE Phase. Does the FDA agree?

FDA Response to Question 25:
Your proposal is acceptable.

Discussion:
None.

Question 26: Does the FDA have feedback on the proposed Communication Plan for managing future interactions?

FDA Response to Question 26:
Your proposal is acceptable.

Discussion:
None.

3.0 ADDITIONAL INFORMATION

PRODUCT QUALITY MICROBIOLOGY COMMENTS

The FDA is providing additional product quality microbiology comments for you to consider during development of your commercial manufacturing process and preparation of your 351(a) BLA submission.

All facilities should be registered with the FDA at the time of the 351(a) BLA submission and ready for inspection in accordance with 21 CFR 600.21 and 601.20(b)(2). Include in the BLA submission a complete list of the manufacturing and testing sites with their corresponding FEI numbers. A preliminary manufacturing schedule for the drug substance and drug product should be provided in the BLA submission to facilitate the planning of pre-license inspections during the review cycle. Manufacturing facilities should be in operation and manufacturing the product under review during the inspection.

Information and data for CMC product quality microbiology should be submitted in the specified sections indicated below.

The CMC Drug Substance section of the 351(a) BLA (Section 3.2.S) should contain information and data summaries for microbial and endotoxin control of the drug substance. The information should include, but not be limited to the following:

- Bioburden and endotoxin levels at critical manufacturing steps should be monitored using qualified bioburden and endotoxin tests. Bioburden sampling should occur prior to any 0.2 µm filtration step. The pre-established bioburden and endotoxin limits should be provided (3.2.S.2.4).
- Bioburden and endotoxin data obtained during manufacture of three process qualification (PPQ) lots (3.2.S.2.5).
- Microbial data from three successful product intermediate hold time validation runs at manufacturing scale. Bioburden and endotoxin levels before and after the maximum allowed hold time should be monitored and bioburden and endotoxin limits provided (3.2.S.2.5).
- Chromatography resin and UF/DF membrane lifetime study protocols and acceptance criteria for bioburden and endotoxin samples. During the lifetime studies, bioburden and endotoxin samples should be taken at the end of storage prior to sanitization (3.2.S.2.5).
- Information and summary results from the shipping validation studies (3.2.S.2.5).
- Drug substance bioburden and endotoxin release specifications (3.2.S.4).
- Summary reports and results from bioburden and endotoxin test method qualification studies performed for in-process intermediates and the drug substance. If compendial test methods are used, brief descriptions of the methods should be provided in addition to the compendial reference numbers (3.2.S.4).

The CMC Drug Product section of the 351(a) BLA (Section 3.2.P) should contain validation data summaries to support the aseptic processing operations. For guidance on the type of data and information that should be submitted, refer to the 1994 FDA Guidance for Industry *"Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products"* available at:

http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm072171.pdf

The following information should be provided in Sections 3.2.P.3.3 and/or 3.2.P.3.4, as appropriate:

- Identification of the manufacturing areas and type of fill line (e.g. open, RABS, isolator), including area classifications.
- Description of the sterilizing filter (supplier, size, membrane material, membrane surface area, etc.); wetting agent used for post-use integrity testing of the sterilizing filter and post-use integrity test acceptance criteria; sterilizing filtration parameters, as validated by the microbial retention study. For sterilizing filtration driven by peristaltic pump, pressure upstream of the filter should be monitored to ensure sterile filtration is performed within validated limits.
- Parameters for filling and capping for the vials.
- A list of all equipment and components that contact the sterile drug product (i.e. the sterile-fluid pathway) with the corresponding method(s) of sterilization and depyrogenation, including process parameters. The list should include single-use equipment.
- Processing and hold time limits, including the time limit for sterilizing filtration and aseptic filling.
- Sampling points and in-process limits for bioburden and endotoxin. Bioburden samples should be taken at the end of the hold time prior to the subsequent filtration step. Pre-sterile filtration bioburden limits should not exceed 10 CFU/100 mL.

The following study protocols and validation data summaries should be included in Section 3.2.P.3.5, as appropriate:

- Bacterial filter retention study for the sterilizing filter. Include a comparison of validation test parameters with routine sterile filtration parameters.
- Sterilization and depyrogenation of equipment and components that contact the sterile drug product. Provide summary data for the three validation studies and describe the equipment and component revalidation program.
- In-process microbial controls and hold times. Three successful product intermediate hold time validation runs should be performed at manufacturing scale, unless an alternative approach can be scientifically justified. Bioburden

and endotoxin levels before and after the maximum allowed hold time should be monitored and bioburden and endotoxin limits provided.

- Isolator decontamination summary data and information, if applicable.
- Three successful consecutive media fill runs, including summary environmental monitoring data obtained during the runs. Describe the environmental and personnel monitoring procedures followed during media fills and compare them to the procedures followed during routine production.
- Information and summary results from shipping validation studies.
- Validation of capping parameters, using a container closure integrity test.

The following product testing and method validation information should be provided in the appropriate sections of Module 3.2.P:

- Container closure integrity testing. System integrity should be demonstrated initially and during stability. Container closure integrity method validation should demonstrate that the assay is sensitive enough to detect breaches that could allow microbial ingress (≤ 20 microns). Container closure integrity testing should be performed *in lieu* of sterility testing for stability samples every 12 months (annually) until expiry.
- Summary report and results for qualification of the bioburden, sterility, and endotoxin test methods performed for in-process intermediates (if applicable) and the finished drug product, as appropriate. If compendial test methods are used, brief descriptions of the methods should be provided in addition to the compendial reference numbers. Provide full descriptions and validation of non-compendial rapid microbial methods.
- Summary report and results of the Rabbit Pyrogen Test conducted on three batches of drug product in accordance with 21 CFR610.13(b).

- Low endotoxin recovery studies. Certain product formulations have been reported to mask the detectability of endotoxin in the USP <85> *Bacterial Endotoxin Test* (BET). The effect of hold time on endotoxin detection should be assessed by spiking a known amount of standard endotoxin (RSE or purified CSE) into undiluted drug product and then testing for recoverable endotoxin over time. Microbiological studies in support of the post-dilution storage conditions. Describe the test methods and results that employ a minimum countable inoculum (10-100 CFU) to simulate potential microbial contamination that may occur during dilution. The test should be run at the label's recommended storage conditions, be conducted for twice the recommended storage period, bracket the drug product concentrations that would be administered to patients, and use the label-recommended diluents. Periodic intermediate sample times are recommended. Challenge organisms may include strains described in USP <51> *Antimicrobial Effectiveness Testing*, plus typical skin flora or species associated with hospital-borne infections. *In lieu* of this data, the product labeling should recommend that the post-dilution storage period is not more than 4 hours.

PRODUCT QUALITY COMMENTS

1. To facilitate the Agency's review of the DS and DP manufacturing processes for lecanemab, provide the information for process parameters and in-process control, as applicable, in the following tabular format. Please provide a separate table for each unit operation. The tables should summarize information from module 3 and may be submitted either to Module 1 or Module 3R.

Process Parameter/Operating Parameter/ In-Process Control	Proven Acceptable Range/ Control Limits/Targets[1] for Commercial Manufacturing Process	Criticality Classification[2]	Characterized Range/ Control Limits/Targets[1] tested in Process Development Studies	Manufactured Range/ Control Limits/Targets[1] used for Pivotal Clinical Study Lots	Manufactured Range/ Control Limits/Targets[1] used in Process Validation	Justification of the Proposed Commercial Acceptable Range[3]	Comment[4]

[1] As applicable
[2] For example, critical process parameter, key process parameter, non-critical process parameter, as described in module 3.
[3] This could be a brief verbal description or links to the appropriate section of the eCTD.
[4] Optional.

2. To facilitate the Agency's review of the control strategy for lecanemab, provide information for quality attributes and process and product related impurities for the DS, and DP in the following tabular format. The tables should summarize information from module 3 and may be submitted either to module 1 or module 3R.

Quality Attr butes and Process and Product Related Impurities for CI, DS and DP	Criticality Classification[1]	Impact[2]	Source[3]	Analytical Method[4]	Proposed Control Strategy[6]	Justification of the Proposed Control Strategy[6]	Comment[7]

[1] For example, critical quality attr bute or non-critical quality attribute.
[2] What is the impact of the attr bute, e.g. contributes to potency, immunogenicity, safety, efficacy.
[3] What is the source of the attribute or impurity, e.g. intrinsic to the molecule, fermentation, protein A column.
[4] List all the methods used to test an attribute in-process, at release, and on stability. For example, if two methods are used to test identity then list both methods for that attr bute.
[5] List all the ways the attr bute is controlled, for example, in-process testing, validated removal, release testing, stability testing.
[6] This could be a brief verbal description or links to the appropriate section of the eCTD.
[7] Optional

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*.[3] 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.[4]

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

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

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*.[5]

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.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

None.

[5] 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.

5.0 ATTACHMENTS AND HANDOUTS

Attached is the slide set provided by Eisai for the September 10, 2021, teleconference.

9 Pages have been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/

ERIC P BASTINGS
10/11/2021 08:23:18 AM

CDER Breakthrough Therapy Designation Determination Review Template (BTDDRT)

IND #	105081
Request Receipt Date	June 3, 2021
Product	Lecanemab (BAN2401)
Indication	Treatment of Alzheimer's disease
Drug Class/Mechanism of Action	Humanized immunoglobulin 1 (IgG1) monoclonal antibody directed against aggregated forms of amyloid beta
Sponsor	Eisai Inc.
ODE/Division	ON/DN1
Breakthrough Therapy Request (BTDR) Goal Date (within 60 days of receipt)	August 2, 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):**

   Treatment of Alzheimer's disease

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.

Lecanemab is a humanized immunoglobulin gamma 1 (IgG1) monoclonal antibody directed against aggregated forms of amyloid beta (protofibrils). It is postulated that clearance of amyloid beta protofibrils neutralizes toxicity to neurons and attenuates the progression of neurodegeneration. Lecanemab is appropriately grouped with a current generation of anti-amyloid antibodies under development (donanemab, aducanumab, and gantenerumab) which have demonstrated robust reductions in brain amyloid as measured by PET and have been associated with early evidence suggesting favorable effects on clinical endpoints.

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

The change from baseline in amyloid signal as measured by ^{18}F-florbetapir PET and quantified by a composite standard uptake value ratio (SUVR) is an endpoint that is reasonably likely to predict clinical benefit and supports accelerated approval. SUVR is a method to estimate brain levels of amyloid beta plaque in composites of brain areas expected to be widely affected by Alzheimer's disease pathology (frontal, parietal, lateral, temporal, sensorimotor, and anterior and posterior cingulate cortices), compared to a brain region expected to be spared of such pathology (cerebellum).

The Clinical Dementia Rating Scale – Sum of Boxes (CDR-SB) assesses 3 domains of cognition (memory, orientation, judgment/problem solving) and 3 domains of function (community affairs, home/hobbies, personal care) using semi-structured interviews with the patient and a reliable companion or informant. CDR-SB is accepted by the Division as an acceptable primary outcome assessment for studies of Alzheimer's disease intended to demonstrate substantial evidence of effectiveness.

The Alzheimer's Disease Assessment Scale – Cognitive Subscale (ADAS-Cog) is a cognitive assessment consisting of clinical ratings and cognitive tasks. The ADAS-Cog is acceptable as a co-primary endpoint or a secondary endpoint.

The Alzheimer's Disease Composite Score (ADCOMS) is a derived composite score derived from selected items of the CDR-SB, ADAS-Cog and Mini-Mental State Examination (MMSE). It is thought to be more sensitive in this patient population, but changes on the scale are challenging to interpret.

Relevant biomarkers are CSF p-Tau and CSF t-Tau, markers of tau pathophysiology and neurodegeneration, respectively.

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:

Aducanumab is approved for the treatment of Alzheimer's disease under accelerated approval based on reduction in amyloid beta plaques observed in patients treated with aducanumab.

Three acetylcholinesterase inhibitor drugs have been approved for the treatment of mild to moderate Alzheimer's disease. There is also one N-methyl-D-aspartate receptor antagonist approved for the treatment of moderate to severe

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		
Namenda® *(memantine)*	Tablet	21487	10/2003	N-methyl-D-aspartate receptor antagonist	Moderate to Severe AD
	Extended release (ER)	22525	6/2010		

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

Each of the 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.

None of the products listed in the table above has been demonstrated to modify the neuropathological course of Alzheimer's disease.

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
(b) (4)	(b) (4)	(b) (4)	
	Aducanumab	Monoclonal antibody against Aβ	Pending

11. Information related to the preliminary clinical evidence:

The preliminary clinical evidence relevant to the designation determination decision is derived from Study 201, a double-blind, parallel-group, placebo-controlled, multicenter, dose-finding study in patients with mild cognitive impairment due to Alzheimer's disease or with mild Alzheimer's disease dementia. Patients were required to be positive for brain amyloid as indicated by either a PET or CSF assessment and have a MMSE score ≥22 at screening. The primary objective was to evaluate efficacy by establishing the dose regimen with at least 90% of the maximum effective dose treatment effect for lecanemab on the ADCOMS at Month 12. Secondary endpoints included the effect of lecanemab on brain amyloid at Month 18 and the efficacy of lecanemab at Month 18 as assessed by clinical endpoints (ADCOMS, CDR-SB, and ADAS-Cog).

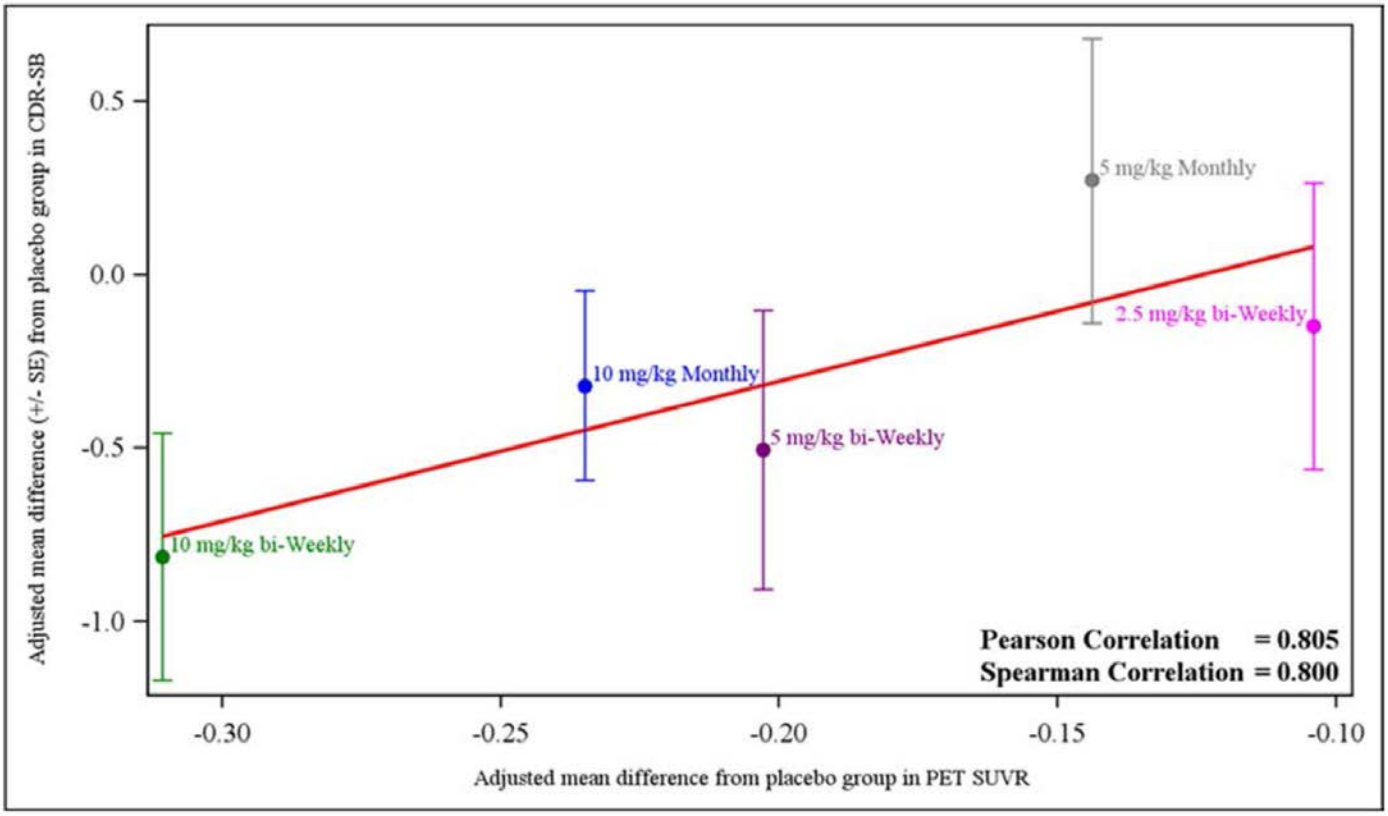
[3] Biweekly reports of all BTDRs, including the sponsor, drug, and indication, are generated and sent to all CPMSs.

Study 201 randomized 856 patients across 6 treatment groups: placebo (n=247), 2.5 mg/kg biweekly (n=52), 5 mg/kg monthly (n=51), 5 mg/kg biweekly (n=92), 10 mg/kg monthly (n=253), or 10 mg/kg biweekly (n=161).

Lecanemab demonstrated a dose- and time-dependent reduction in brain amyloid across all doses compared to placebo. Mean reductions of 0.21 and 0.32 were observed for SUVR after 18 months of lecanemab treatment for the 10 mg/kg monthly and 10 mg/kg biweekly doses, respectively.

The primary endpoint was Bayesian analysis of 12-month clinical change on ADCOMS, which required an 80% probability of >25% clinical reduction in decline versus placebo. At 12 months, the 10 mg/kg biweekly arm had 64% probability to be better than placebo by 25% , which missed the 80% threshold for the primary outcome. For the Bayesian analysis of CDR-SB at Month 18, the probability of lecanemab being superior to placebo was 94.1% and 96.4% for the 10 mg/kg monthly and 10 mg/kg biweekly doses and the treatment difference from placebo was 26% and 33% less decline, respectively. For the MMRM analysis, the mean difference of the combined lecanemab 10 mg/kg dose groups from placebo was -0.302 (p=0.119, 90% CI: -0.620, 0.017), representing a 21% less decline than on placebo.

Reduction in brain amyloid as measured by SUVR was associated with an increased treatment effect on CDR-SB (correlation coefficient = 0.805) as illustrated in the figure below.



Interpretation of the data is complicated by the fact that in response to a request made by European Health Authorities, the sponsor agreed to stop randomizing all ApoE4 carriers to the top dose of 10 mg/kg biweekly in all countries and discontinue all ApoE4 carriers already randomized to 10 mg/kg biweekly with less than 6 months of exposure to lecanemab. Therefore, the top dose includes a higher proportion of ApoE4 non-carriers than other treatment groups.

Safety

The primary safety event identified in clinical trials is amyloid imaging abnormalities (ARIA) which represent a spectrum of imaging findings on brain MRI. These findings include brain edema and brain microhemorrhage. Most

patients who experience ARIA do not have symptoms, and when symptoms occur, they are usually mild or moderate. ARIA is a known consequence of anti-amyloid treatment and is mitigated by dose suspensions and discontinuations and MRI monitoring.

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

☒ GRANT:

Provide brief summary of rationale for granting:

Alzheimer's disease is a serious condition, and lecanemab, unlike available therapies, is targeted at an underlying, fundamental, and defining pathophysiological feature of the disease, with the potential to alter the inescapable and relentless progression of this disease. The clinical data that exist suggest that an alteration in such progression, assessed as a reduction in clinical decline over a prolonged period of time, is an anticipated benefit of lecanemab. A surrogate outcome for which there is substantial evidence of effectiveness, reduction in amyloid beta plaques on PET imaging, has been assessed in the lecanemab development program, and is reasonably likely to predict clinical benefit, as demonstrated by the relationship of amyloid plaque reduction to clinical outcome. An analysis of currently available data from several anti-amyloid antibodies under development demonstrate a clear relationship between reduction of amyloid beta plaque burden in brain and preservation of clinical function. On face, data on SUVR and clinical endpoints in Study 201 support this relationship. There are no safety issues that would preclude the granting of breakthrough therapy designation to lecanemab.

☐ 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:

The sponsor currently has an ongoing placebo-controlled, double-blind, parallel-group, 18-month study (Study 301) to confirm the safety and efficacy of lecanemab in a similar population as Study 201. The study is expected to complete in September 2022. The Division has not yet had a discussion with the sponsor regarding considerations for accelerated approval.

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

APPEARS THIS WAY ON ORIGINAL

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/

KEVIN M KRUDYS
06/21/2021 05:00:44 PM

TERESA J BURACCHIO
06/21/2021 05:19:33 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 105081

MEETING MINUTES

Eisai, Inc.
Attention: Heather Bradley, MPH
Senior Director, Global Regulatory Affairs
100 Tice Boulevard
Woodcliff Lake, NJ 07676

Dear Ms. Bradley:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for BAN2401 (anti-amyloid protofibril monoclonal antibody).

We also refer to the meeting between representatives of your firm and the FDA on October 9, 2018. The purpose of the meeting was to discuss the ongoing development of BAN2401.

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

If you have any questions, call E. Andrew Papanastasiou, Regulatory Project Manager, at (301) 796-1930.

Sincerely,

{See appended electronic signature page}

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

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	B
Meeting Category:	End of Phase 2
Meeting Date and Time:	October 9, 2018, from 3:00 PM to 4:00 PM EDT
Meeting Location:	FDA White Oak
Application Number:	105081
Product Name:	BAN2401
Indication:	Treatment of early Alzheimer's disease (see "Background" below)
Sponsor/Applicant Name:	Eisai, Inc.

FDA ATTENDEES

Billy Dunn, MD - Director, DNP
Eric Bastings, MD - Deputy Director, DNP
Nick Kozauer, MD - Associate Director, DNP
Ranjit Mani, MD - Clinical Reviewer
Kun Jin, PhD - Biostatistics Team Leader
Tristan Massie, PhD - Statistical Reviewer
Jagan Parepally, PhD - Clinical Pharmacology Reviewer
Angela Men, PhD - Clinical Pharmacology Team Leader
E. Andrew Papanastasiou, PharmD, MS - Regulatory Project Manager

SPONSOR ATTENDEES

Lynn Kramer, MD, FAAN - Chief Clinical and Medical Officer, Eisai
Johan Luthman, DDS, PhD - VP, Neurology Clinical Development, Eisai
Shobha Dhadda, PhD - VP, Biostatistics and Clinical Development Operations, Eisai
Chad Swanson, PhD - Senior Director, Clinical Research, Eisai
Martin Rabe, MSc - Vice President, Global Regulatory Strategy, Eisai
Heather Bradley, MPH - Senior Director, Global Regulatory Strategy, Eisai
Mark Hodgkinson - Senior Manager, Global Regulatory Strategy, Eisai
Tsuyoshi Kobayashi Associate - Director, Japan Regulatory Affairs, Eisai
Jim Ferry, PhD - VP, Clinical Pharmacology and Translational Medicine, Eisai
Larisa Reyderman, PhD - Executive Director, Clinical Pharmacology, Eisai
Thomas Visalli, - PhD Director, Nonclinical Regulatory Affairs, Eisai
(b) (4)
Samantha Budd Haeberlein, PhD - VP, Clinical Development, Biogen
Charbel Haber - VP, Regulatory Affairs, Biogen

1. BACKGROUND

BAN2401 is a humanized immunoglobulin G1 (IgG1) monoclonal antibody directed against soluble amyloid beta (Aβ). This product has been developed under the current Investigational New Drug Application (IND), which has been active since July 29, 2010. The proposed indication for BAN2401 is for the treatment of mild cognitive impairment due to Alzheimer's disease and mild Alzheimer's disease dementia.

The objective of this End-of-Phase 2 meeting is to discuss data from a Phase 2 study of BAN2401, Study BAN2401-G000-201 (Study 201), and consideration of registration of this product under the Accelerated Approval pathway to be followed by a Phase 3 efficacy study of this product that is to be conducted post-approval.

Study 201 was begun after the initial IND study, Study BAN2401-G000-101 (Study 101), was conducted. Study 101 was a single and multiple ascending dose study conducted in patients with mild to moderate Alzheimer's disease.

The main objective of Study 201 is to investigate the efficacy and safety of BAN2401 in patients with early Alzheimer's disease (corresponding to patients with mild cognitive impairment due to Alzheimer's disease and mild dementia due to Alzheimer's disease). Study 201 consists of an initial now-complete randomized, double-blind, placebo-controlled, parallel-arm phase with a duration of 18 months to be followed by an open-label extension phase where the administration of BAN2401 may continue for a further 60 months. 856 patients, who conformed to the National Institute on Aging-Alzheimer's Association (NIA-AA) criteria for mild cognitive impairment due to Alzheimer's disease or mild dementia due to Alzheimer's disease, were randomized to six treatment groups in parallel: placebo and five separate BAN2401 dose groups (2.5 mg/kg biweekly, 5.0 mg/kg monthly, 5.0 mg/kg biweekly, 10.0 mg/kg monthly, and 10.0 mg/kg biweekly). Bayesian response adaptive randomization was used in the initial phase of this study through a series of interim analyses conducted on the primary efficacy measure (see below) under the supervision of an independent monitoring committee; as a result of that process, the number of patients randomized to each of the two highest BAN2401 dose groups was higher than that randomized to the three lower BAN2401 treatment groups. Other events influencing randomization also occurred during the course of this study.

The salient outcome measures for the initial 18-month phase of Study 201 were as follows. The primary efficacy parameter was derived from the so-called Alzheimer's Disease Composite Score (ADCOMS) at 12 months. The ADCOMS is in turn derived from selected scores on three commonly-used efficacy instruments: the Alzheimer's Disease Assessment Scale – Cognitive (ADAS-Cog), Clinical Dementia Rating Scale (CDR), and the Mini-Mental Status Examination (MMSE). Key secondary efficacy measures consisted of the change from baseline to Month 18 on each of the following: ADCOMS, Clinical Dementia Rating Scale – Sum of Boxes (CDR-SB), ADAS-Cog, MMSE, brain amyloid load as measured by positron emission tomography, total hippocampal volume as measured by magnetic resonance imaging (MRI), and cerebrospinal fluid concentrations of $A\beta_{1-42}$, total tau, and phosphorylated tau. The safety of BAN2401 was

assessed based on data for adverse events, vital signs, safety laboratory tests, electrocardiograms, safety brain MRI, physical examinations, and the Columbia-Suicide Severity Rating Scale.

The sponsor's conclusions based on the review of efficacy and safety data for the initial 18-month randomized, double-blind, placebo-controlled, parallel-arm phase of this study included the following: the pre-specified criterion for success (at Month 12) on the primary efficacy analysis was not met; a dose-dependent reduction in brain amyloid, relative to placebo, was seen across all the BAN2401 dose arms at Months 12 and 18; a dose-dependent effect of BAN2401 on the ADCOMS, ADAS-Cog, and CDR-SB was seen at Month 18; a dose-dependent effect of BAN2401 on cerebrospinal fluid $A\beta_{1-42}$ and total tau concentrations was also present; and the incidence of adverse events and serious adverse events was similar between the BAN2401 and placebo groups and consistent with the population are study. The sponsor has further concluded that most instances of amyloid-related imaging abnormalities with edema (ARIA-E) that occurred during the study were mild to moderate in severity on MRI and asymptomatic, appeared during the first 3 months of treatment, and typically resolved within 4 to 12 weeks.

In the sponsor's view, the effects of BAN2401 in Study 201 on the ADCOMS (as a surrogate clinical endpoint) and on brain amyloid load as measured by positron emission tomography (as a biomarker endpoint) are reasonably likely to predict clinical benefit and thus support the accelerated approval of BAN2401 for the proposed indication, with a Phase 3 efficacy and safety study to be conducted post approval.

The main phase of the proposed post approval Phase 3 study would have a randomized, double-blind, placebo-controlled, parallel-arm design and an 18-month duration; an open-label extension would follow. In the main phase of that study, 990 patients with either mild cognitive impairment due to Alzheimer's disease or mild dementia due to Alzheimer's disease (as defined by NIA-AA criteria) would be randomized to 2 treatment groups: BAN2401 in a dose of 10 mg/kg bi-weekly, and placebo. The primary efficacy parameter (b) (4) Key secondary efficacy parameters would be the change from baseline to Month 18 in brain amyloid load (as measured by positron emission tomography) and in the 14-item version of the ADAS-Cog. The safety of BAN2401 in this study would be assessed based on the following: adverse events, vital signs, safety laboratory tests, safety MRI, and electrocardiograms.

This meeting is also directed at discussing the following issues that are described further in this submission: whether the data for Study 201 support Breakthrough Therapy Designation for BAN2401; whether the completed and ongoing clinical pharmacology investigations of BAN2401 support accelerated approval; the acceptability of a proposed pharmacokinetic modeling and simulation plan for BAN2401; the extent of the clinical safety database required to support accelerated approval; and the nonclinical data required to support a Biologics License Application (BLA) for BAN2401.

FDA sent Preliminary Comments to Eisai on October 5, 2018

2. DISCUSSION

Introductory Statement

This introductory statement is directed at addressing a number of your individual questions, fully or in part.

We have significant concerns about your interpretation of the clinical efficacy data for Study BAN2401-G000-201 (Study 201). You have concluded that evidence for the efficacy of BAN2401 on several clinical outcome measures in that study was apparent or most apparent at the BAN2401 dose of 10 mg/kg biweekly, in comparison with placebo. Preliminary concerns that we have been able to identify, even through our limited assessment of the data included in your meeting package, are in regard to the following: its unusual design and complicated conduct; the substantial proportion of patients in the two highest BAN2401 dose groups that had missing efficacy data at the 12-month and 18-month timepoints with the additional implications of such missing data; the post hoc nature of many of the analyses that you have conducted; the absence of any correction for multiplicity in those many analyses; and the disproportion in ApoE4 carriers between the BAN2401 10 mg/kg bi-weekly group and the placebo group. We are also concerned that the mixed model for repeated measures approach that you have used in your analyses may not be valid under a Bayesian response adaptive randomization design.

Your presentation in this meeting package does draw attention to an apparently robust effect, that is dose-dependent and extends across all doses of BAN2401 investigated, on brain amyloid load, as measured by standard uptake value ratios derived from positron emission tomography. However, given our concerns about the validity of the conclusions that you have reached using the clinical efficacy data for Study 201, we have doubts about the clinical implications of the effect of BAN2401 on brain amyloid load that you have described. As you are aware, several clinical development programs of other compounds in Alzheimer's disease have failed to demonstrate an effect on clinical outcomes, despite an apparent reduction in brain amyloid having been demonstrated either on positron emission tomography or cerebrospinal fluid examination. It is not clear that the effect of BAN2401 on brain amyloid may be better predictive of a positive clinical efficacy outcome than in other development program.

Accordingly, based on the information available to us at this time, we do not agree with your proposal that BAN2401 qualifies for accelerated approval based on the results of Study 201. For the same reasons, we are even less able to agree that the results of Study 201 provide substantial evidence to support the standard approval of BAN2401 for the indication that you are currently seeking.

We also have a number of reservations about the use of the ADCOMS as a clinical efficacy measure. These are as follows.

- The values of the weights assigned to the different components of the ADCOMS are database- and method-dependent and are therefore estimates at best. In addition, we

are unaware of any patient or clinical surveys having been conducted to justify the unequal item weights and their relative and very precise differences.

- An increase in the sensitivity of a scale should be balanced by ensuring that aspects of a disease important to patients and their caregivers are not minimized. The use of unequal weights in the ADCOMS with the differences among item weights varying widely (e.g., with small fractional differences in weight in some instances and five-fold differences in weight in others) may impede clinical interpretability and unintentionally minimize important aspects of the disease.

- We are concerned about the numerical method used to derive the ADCOMS that is described in a publication that you have cited (Wang J et al. ADCOMS: a composite clinical outcome for prodromal Alzheimer's disease trials. J Neurol Neurosurg Psychiatry. 2016;87:993-999).

We do not concur with the design of your proposed Phase 3 study, (b) (4) and do not find such a proposal acceptable. Moreover, given our current doubts about whether the clinical efficacy data for Study 201 are consistent with the conclusions that you have reached, you should be prepared to conduct an adequate and well-controlled efficacy study of BAN2401 in early Alzheimer's disease and to substantiate the results of that study if positive (in a further adequate and well-controlled study) prior to the initial approval of BAN2401. The exceptional circumstances under which the results of a single adequate and well-controlled study may suffice to support the approval of a drug or biologic for a specific indication are discussed in the Agency Guidance for Industry document entitled "*Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products*," available at the following link.

https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm072008.pdf

We recognize that in this meeting package you may have already attempted to address at least some of the concerns that we have raised above. Nonetheless, those concerns remain.

We are open to a further discussion of the above concerns. To enable that discussion, we encourage you to submit to your IND a more complete and more systematically-organized description of the data for Study 201 than that included in the current submission, including a fully detailed description of study results at all doses studied. That submission should also attempt to address our current concerns.

Question 1: Eisai considers the clinical and biomarker efficacy of BAN2401 as demonstrated in Study 201 as reasonably likely to predict clinical benefit and therefore eligible for Accelerated Approval of BAN2401 as treatment for early AD. Does the Division agree?

FDA Response to Question 1:
Please see the Introductory Statement above.

Meeting Discussion:
The sponsor had a number of comments in response to those put forward by the Agency in the above introductory statement. Those sponsor comments are summarized below, but were expanded upon during the discussion and were assisted by the contents of a slide presentation (see attached slides). In the sponsor's opinion:

- The effects that were seen on clinical and biomarker outcomes in Study 201, when viewed together, support the accelerated approval of BAN2401 for the treatment of mildly-impaired patients with Alzheimer's disease. Brain amyloid load (as measured by positron emission tomography) and the ADCOMS are, respectively, surrogate and intermediate clinical endpoints that are reasonably likely to predict clinical benefit.

- The design and conduct of Study 201 satisfied the main principles described in the Agency draft Guidance for Industry entitled "*Adaptive Designs for Clinical Trials of Drugs and Biologics*" (September 2018) extending to prespecified Bayesian response adaptive randomization and interim analyses, preservation of the Type I error, and maintenance of the integrity of the study.

- Several separate analytical approaches (Bayesian and frequentist analyses; pharmacokinetic-pharmacodynamic correlation) using a variety of models demonstrated consistent treatment effects on a number of clinical outcomes (ADCOMS, ADAS-Cog, CDR-SB, and MMSE) and biomarker measures (cerebrospinal fluid $A\beta_{42}$, total tau, p-tau, neurogranin, and neurofilament light chain concentrations). The treatment effects on several clinical outcomes correlated with each other.

- Simulations indicate that the temporary halt in randomization of all ApoE4-positive subjects to the BAN2401 10 mg/kg biweekly dose that was imposed by regulatory authorities in the European Union under the Voluntary Harmonization procedure may have introduced a strong bias such that the efficacy of BAN2401 was less apparent in Study 201 than it may otherwise have been.

- While Study 201 did not meet its prespecified criterion for efficacy on the primary efficacy analysis at Month 12, that criterion had set a high bar for achieving efficacy, and the other effects seen (on clinical and biomarker outcomes) in that study, some of which were observed early and remained sustained, were reasonably likely to predict clinical benefit.

- The p-values seen on various post-hoc analyses were indeed nominally statistically significant.

The sponsor also acknowledged the Agency's concerns about the use of the ADCOMS as an outcome measure.

The data that were presented by the sponsor in support of the above comments included those from analyses that were performed very recently and were not described in the meeting package.

In response, the Agency made the following comments:

1. The available efficacy data for Study 201 are not adequate to support accelerated approval of BAN2401 for the proposed indication.

2. A determination of whether data such as those presented could be supportive of accelerated approval on BAN2401 will be based not so much on the totality of such data, but on whether a specific biomarker or intermediate clinical endpoint was reasonably likely to predict clinical benefit.

3. While the data presented for Study 201 may, on face, indicate that BAN2401 reduces brain amyloid, the clinical implications of that effect are unclear. The Agency had considerable difficulty confirming that the clinical efficacy data for Study 201, as described in this meeting package, were consistent with the sponsor's assertions. This difficulty stemmed from the incompleteness of the data (examples of items that were lacking were provided by the Agency), and several apparent inconsistencies between clinical and biomarker effects, among other deficiencies.

Several aspects of the statistical analyses that were performed were further discussed between the Agency and sponsor. In response to a question from the Agency, the sponsor indicated that a total of 17 interim analyses were performed during the study. The Agency observed that with so many interim analyses having been performed, the interpretation of the results of efficacy analyses that were based on a mixed model for repeated measures approach could be problematic; the sponsor too agreed that such results should be interpreted cautiously. The Agency also noted that Study 201 was developed as a proof-of-concept study and had a complex statistical analysis plan; for those reasons, as well as those already stated under #3 above, the Agency's preliminary comments could not fully address several aspects of the efficacy analyses that were conducted and the interpretation of their results.

The Agency recommended that further discussions be held between the Agency and sponsor. Each of those discussions should be preceded by a submission from the sponsor addressing a specific subject, as further described below:

- The first of those submissions should discuss the proposed mechanism of action of BAN2401 in Alzheimer's disease and focus on explaining why, under that mechanism, an effect of that compound on brain amyloid may be more predictive of

clinical efficacy than has been the case with other anti-amyloid agents that have been under development.

- The second of those submissions should contain a comprehensive and well-organized presentation of all efficacy data available for Study 201, including data for both clinical and biomarker outcomes, with data supporting the performance characteristics of the assay. The discussion of the efficacy data would take place over 2 or 3 separate meetings, with topics identified in advance. Submission of efficacy datasets may be requested as part of these discussions.

An additional subject for discussion is the design of a Phase 3 efficacy study of BAN2401. The Agency recommended that the full protocol for that study be submitted formally as soon as possible to IND 105081, with a request for Agency review and comment, and that the study be then commenced promptly. A highly abbreviated outline of such a study was included in the sponsor's presentation at the meeting and differed somewhat from the outline for that study included in the meeting package. The study proposed at the meeting is to have a randomized, double-blind, placebo-controlled, parallel-arm initial phase lasting 18 months, to be followed by a two-year open-label extension. The study is to have 2 treatment arms: BAN2401 and placebo. The inclusion criteria for that study will be similar to those for Study 201. The primary efficacy measure will be the CDR-SB, with the secondary efficacy measures consisting of the ADCOMS, ADAS-Cog, and CDR.

***Question 2*:** Does the Division agree that Study 201 provides substantial evidence of efficacy for BAN2401 10 mg/kg biweekly as treatment of MCI due to AD and mild AD dementia (early AD)?

FDA Response to Question 2:
Please see the Introductory Statement above.

Meeting Discussion:
Please see the discussion under Question 1 above.

Question 3: Does the Division consider data from Study 201, supported by independent data from other compounds, as evidence that amyloid PET correlated with positive clinical findings is an appropriate biomarker to support the amyloid hypothesis for disease modification in early AD?

FDA Response to Question 3:
Please see the Introductory Statement above. The extent to which data obtained independently from development programs of other compounds that have a mechanism of action that is hypothesized to be similar to BAN2401 are relevant to BAN2401 is unclear.

Meeting Discussion:
Please see the discussion under Question 1 above.

Question 4: Does the Division agree that Study 201 data demonstrate modification of underlying disease pathophysiology in early AD (correlation of reduction in brain amyloid load via PET and slowing of clinical decline via ADCOMS, ADAS-cog, & CDR-SB)?

FDA Response to Question 4:
Please see the Introductory Statement above.

Meeting Discussion:
Please see the discussion under Question 1 above.

Question 5: Does the Agency consider the ADCOMS endpoint to be an appropriate clinical outcome measure in an early AD population? If not, what additional data beyond Study 201 would be required to support the use of ADCOMS as an appropriate clinical outcomes measure?

FDA Response to Question 5:
Please see the Introductory Statement above.

Meeting Discussion:
Please see the discussion under Question 1 above.

Question 6: Does the Division agree with the proposed design and patient population for the post-approval/phase 3 study?

FDA Response to Question 6:
Please see the Introductory Statement above.

Meeting Discussion:
Please see the discussion under Question 1 above.

Question 7: Does the Division agree with the proposed post-approval/Phase 3 safety monitoring plan?

FDA Response to Question 7:
The safety monitoring plan for your proposed Phase 3 study is in itself acceptable in form, subject to our review of the full protocol for that study. However, please also see the Introductory Statement above.

Meeting Discussion:
Please see the discussion under Question 1 above.

Question 8: Can the Division confirm that the anticipated clinical safety database expected for BAN2401 is sufficient to support submission and review of a BLA under Accelerated Approval?

FDA Response to Question 8:
Please see our Introductory Statement above, in which we have stated that the available data do not appear to support the accelerated approval of BAN2401.

Meeting Discussion:
Please see the discussion under Question 1 above.

Question 9: Does the Division agree that Study 201 provides sufficient data to support an application for Breakthrough Therapy Designation (BTD)?

FDA Response to Question 9:
Please see the Introductory Statement above. Based on our preliminary assessment, it appears unlikely that BAN2401 would qualify for Breakthrough Therapy Designation.

Meeting Discussion:
None.

Post-Meeting Comment:
Prior to this meeting, a teleconference had been scheduled between the Agency and sponsor at which the possibility of a Breakthrough Therapy Designation for BAN2401 was to be preliminarily discussed. Based on the Agency assessment described in the preliminary response to this question and the meeting discussion summarized under the "Introductory Statement" heading above, it remains unlikely that BAN2401 would qualify for Breakthrough Therapy Designation at the present time. Accordingly, that teleconference has been canceled.

Question 10: Does the Division agree that the clinical pharmacology evaluation of BAN2401is sufficient to support a BLA under Accelerated Approval?

FDA Response to Question 10:
Please see our Introductory Statement above, in which we have stated that the available data do not appear to support the accelerated approval of BAN2401.

Meeting Discussion:
Please see the discussion under Question 1 above.

Question 11: Does the Division agree with (or could the Division comment on) the proposed Modeling and Simulation Plan for BAN2401?

FDA Response to Question 11:
Your proposed modeling and simulation plan for BAN2401 appears reasonable.

Meeting Discussion:
The Agency will further review additional pharmacokinetic data (including data for pharmacokinetic-pharmacodynamic correlation analyses) presented at the meeting, with comments on those data to be included in the meeting minutes.

Post-Meeting Comment:
The Agency has reviewed the additional pharmacokinetic data presented at the meeting and has no further comments.

Question 12: Does the Division agree that the completed nonclinical pharmacology and toxicology evaluation of BAN2401 are sufficient to support review of a BLA?

FDA Response to Question 12:
Based on the information provided in the briefing document, the completed nonclinical studies remain sufficient to support submission of a BLA for the use of BAN2401 in patients ≥ 50 years of age.

Meeting Discussion:
None.

MICROBIOLOGY COMMENTS:
(The following are additional post-meeting comments for your consideration).

The Agency is providing additional product quality microbiology comments for you to consider during development of your commercial manufacturing process and preparation of your 351(a) Biologics License Application (BLA) submission.

All facilities should be registered with the FDA at the time of the 351(a) BLA submission and ready for inspection in accordance with 21 CFR 600.21 and 601.20(b)(2). You should include in the BLA submission a complete list of the manufacturing and testing sites with their corresponding Federal Establishment Identification (FEI) numbers. A preliminary manufacturing schedule for the drug substance and drug product should be provided in the BLA submission to facilitate the planning of pre-license inspections during the review cycle. Manufacturing facilities should be in operation and manufacturing the product under review during the inspection.

Information and data for Chemistry, Manufacturing, and Controls (CMC) product quality microbiology should be submitted in the specified sections indicated below.

The CMC Drug Substance section of the 351(a) BLA (Section 3.2.S) should contain information and data summaries for microbial and endotoxin control of the drug substance. The information should include, but not be limited to, the following:

- Bioburden and endotoxin levels at critical manufacturing steps should be monitored using qualified bioburden and endotoxin tests. Bioburden sampling should occur prior to any 0.2 µm filtration step. The pre-established bioburden and endotoxin limits should be provided (3.2.S.2.4).
- Bioburden and endotoxin data obtained during manufacture of three process qualification (PPQ) lots (3.2.S.2.5).
- Microbial data from three successful product intermediate hold time validation runs at manufacturing scale. Bioburden and endotoxin levels before and after the maximum allowed hold time should be monitored and bioburden and endotoxin limits provided (3.2.S.2.5).
- Chromatography resin and ultrafiltration/diafiltration (UF/DF) membrane lifetime study protocols and acceptance criteria for bioburden and endotoxin samples. During the lifetime studies, bioburden and endotoxin samples should be taken at the end of storage prior to sanitization (3.2.S.2.5).
- Information and summary results from the shipping validation studies (3.2.S.2.5).
- Drug substance bioburden and endotoxin release specifications (3.2.S.4).
- Summary reports and results from bioburden and endotoxin test method qualification studies performed for in-process intermediates and the drug substance. If compendial test methods are used, brief descriptions of the methods should be provided in addition to the compendial reference numbers (3.2.S.4).

The CMC Drug Product section of the 351(a) BLA (Section 3.2.P) should contain validation data summaries to support the aseptic processing operations. For guidance on the type of data and information that should be submitted, please refer to the 1994 FDA Guidance for Industry entitled, *"Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products"* which is available at:

http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm072171.pdf.

The following information should be provided in Sections 3.2.P.3.3 and/or 3.2.P.3.4, as appropriate.

- Identification of the manufacturing areas and type of fill line (e.g. open, restricted access barrier systems [RABS], isolator), including area classifications.
- Description of the sterilizing filter (supplier, size, membrane material, membrane surface area, etc.); sterilizing filtration parameters (pressure and/or flow rate), as validated by the microbial retention study; wetting agent used for post-use integrity testing of the sterilizing filter and post-use integrity test acceptance criteria.
- Parameters for filling and capping for the vials.
- A list of all equipment and components that contact the sterile drug product (i.e. the sterile-fluid pathway) with the corresponding method(s) of sterilization and depyrogenation, including process parameters. The list should include single-use equipment.
- Processing and hold time limits, including the time limit for sterilizing filtration and aseptic filling.
- Sampling points and in-process limits for bioburden and endotoxin. Bioburden samples should be taken at the end of the hold time prior to the subsequent filtration step. Pre-sterile filtration bioburden limits should not exceed 10 CFU/100 mL.

The following study protocols and validation data summaries should be included in Section 3.2.P.3.5, as appropriate:

- Bacterial filter retention study for the sterilizing filter. Include a comparison of validation test parameters with routine sterile filtration parameters.
- Sterilization and depyrogenation of equipment and components that contact the sterile drug product. Provide summary data for the three validation studies and describe the equipment and component revalidation program.
- In-process microbial controls and hold times. Three successful product intermediate hold time validation runs should be performed at manufacturing scale, unless an alternative approach can be scientifically justified. Bioburden and endotoxin levels before and after the maximum allowed hold time should be monitored and bioburden and endotoxin limits provided.
- Isolator decontamination summary data and information, if applicable.
- Three successful consecutive media fill runs, including summary environmental monitoring data obtained during the runs. Describe the environmental and personnel monitoring procedures followed during media fills and compare them to the procedures followed during routine production.
- Information and summary results from shipping validation studies.
- Validation of capping parameters, using a container closure integrity test.

The following product testing and method validation information should be provided in the appropriate sections of Module 3.2.P:

- Container closure integrity testing. System integrity should be demonstrated initially and during stability. Container closure integrity method validation should demonstrate that the assay is sensitive enough to detect breaches that could allow microbial ingress (≤ 20 microns). Container closure integrity testing should be performed *in lieu* of sterility testing for stability samples every 12 months (annually) until expiry.
- Summary report and results for qualification of the bioburden, sterility, and endotoxin test methods performed for in-process intermediates (if applicable) and the finished drug product, as appropriate. If compendial test methods are used, brief descriptions of the methods should be provided in addition to the compendial reference numbers. You should provide full descriptions and validation of non-compendial rapid microbial methods.
- Summary report and results of the Rabbit Pyrogen Test conducted on three batches of drug product in accordance with 21 CFR 610.13(b).
- Low endotoxin recovery studies. Certain product formulations have been reported to mask the detectability of endotoxin in the USP <85> *Bacterial Endotoxin Test* (BET). The effect of hold time on endotoxin detection should be assessed by spiking a known amount of standard endotoxin (reference standard endotoxin [RSE] or purified controlled standard endotoxin [CSE]) into undiluted drug product and then testing for recoverable endotoxin over time. Low endotoxin recovery studies may not be necessary for products that do not contain polysorbate.

4. 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* at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email Pedsdrugs@fda.hhs.gov. For further guidance on pediatric product development, please refer to: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm.

DATA STANDARDS FOR STUDIES

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

On December 17, 2014, FDA issued final guidance, *Providing Electronic Submissions in Electronic Format--- Standardized Study Data* (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292334.pdf). This guidance describes the submission types, the standardized study data requirements, and when standardized study data will be required. Further, it describes the availability of implementation support in the form of a technical specifications document, Study Data Technical Conformance Guide (Conformance Guide) (See http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf), as well as email access to the eData Team (cder-edata@fda.hhs.gov) for specific questions related to study data standards. Standardized study data will be required in marketing application submissions for clinical and nonclinical studies that start after December 17, 2016. Standardized study data will be required in commercial IND application submissions for clinical and nonclinical studies that start after December 17, 2017. CDER has produced a *Study Data Standards Resources* web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers.

Although the submission of study data in conformance to the standards listed in the FDA Data Standards Catalog will not be required in studies that start on or before December 17, 2016, CDER strongly encourages IND sponsors to use the FDA supported data standards for the

submission of IND applications and marketing applications. The implementation of data standards should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. For clinical and nonclinical studies, IND sponsors should include a plan (e.g., in the IND) describing the submission of standardized study data to FDA. This study data standardization plan (see the Conformance Guide) will assist FDA in identifying potential data standardization issues early in the development program.

Additional information can be found at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm.

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 and the CDER/CBER Position on Use of SI Units for Lab Tests website found at https://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM587505.pdf.

SUBMISSION FORMAT REQUIREMENTS

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

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

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*, available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf.

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 (available at: https://www.fda.gov/downloads/regulatoryinformation/guidances/ucm126396.pdf) and for more information.

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

5. ATTACHMENTS AND HANDOUTS

Slides presented by Eisai on October 9, 2018, during the meeting with the Agency, are attached.

12 Pages have been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/

ERIC P BASTINGS
11/08/2018