CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

761269Orig1s001

Trade Name:	Leqembi injection
Generic or Proper Name:	lecanemab-irmb
Sponsor:	Eisai Inc.
Approval Date:	July 6, 2023
Indication:	LEQEMBI is indicated for the treatment of Alzheimer's disease. Treatment with LEQEMBI should be initiated in patients with mild cognitive impairment or mild dementia stage of disease, the population in which treatment was initiated in clinical trials.

CENTER FOR DRUG EVALUATION AND RESEARCH

761269Orig1s001

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761269Orig1s001

APPROVAL LETTER

BLA 761269/S-001

GENERAL ADVICE
CORRECTION OF POSTMARKETING REQUIREMENT (PMR)
AND POSTMARKETING COMMITMENT (PMC) SET/NUMBERS

Eisai Inc.
Attention: Stacie P. O'Sullivan
Director, Global Regulatory Strategy
200 Metro Boulevard
Nutley, NJ 07110

Dear Ms. O'Sullivan:

Please refer to your supplemental biologics license application (sBLA), dated and received on January 6, 2023, and your amendments, submitted under section 351(a) of the Public Health Service Act for Leqembi (lecanemab-irmb) injection.

We also refer to your BLA Supplement Approval letter issued July 6, 2023.

The purpose of this letter is to provide you with new PMR/PMC set and numbers for the 505(o)(3) PMRs and non-reportable PMC listed in the July 6, 2023, Approval letter. Please reference the PMR/PMC set and numbers listed below when reporting on or referencing these PMRs and PMC instead of those listed in the July 6, 2023, Approval letter.

POSTMARKETING REQUIREMENTS UNDER 505(o)

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

Since Leqembi was approved on January 6, 2023, we have become aware of clinical trial data showing an increased risk of symptomatic, serious, and severe radiographic amyloid related imaging abnormalities (ARIA) in ApoE ε4 homozygotes who are treated with Leqembi compared to heterozygotes and noncarriers. We have also become aware of clinical trial data showing intracerebral hemorrhage greater than 1 cm in patients taking Leqembi who have risk factors for intracerebral hemorrhage that include findings on neuroimaging suggestive of cerebral amyloid angiopathy (CAA) and use of anticoagulants. We consider this information to be "new safety information" as defined in section 505-1(b)(3) of the FDCA.

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

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

4497-1 Conduct a registry-based, prospective, observational study to evaluate clinical safety outcomes among Alzheimer's disease patients treated with lecanemab-irmb, using, for example, the Alzheimer's Network for Treatment and Diagnostics (ALZ-NET) registry, including patients who are ApoE ε4 homozygotes, and/or exposed to antithrombotics, and/or have a diagnosis of, or imaging findings consistent with a high risk for, cerebral amyloid angiopathy. The primary clinical safety outcomes should include amyloid related imaging abnormalities (ARIA)-edema (ARIA-E), and ARIA hemosiderin deposition (ARIA-H) and any associated clinical symptoms, and intracerebral hemorrhage >1 cm in size. Additional outcomes of interest should also include seizures, anaphylaxis, and death. Baseline characterization of the registry population should include demographic data, diagnosis and stage of disease, ApoE genotype, baseline MRI findings (e.g., microhemorrhages, evidence of cerebral amyloid angiography or other imaging findings consistent with high risk of cerebral amyloid angiography, etc.), other biomarkers that are potential predictors of disease course or adverse outcomes, and prior medications including prior Alzheimer's disease (AD) therapy and antithrombotic therapy. The registry should also collect information on concomitant medications (e.g., antiplatelet and antithrombotic drugs, other AD treatments). When available, the study should provide a comparison of safety outcomes to estimated background rates in an appropriate comparator population.

The timetable you submitted on July 5, 2023, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	03/2024
Final Protocol Submission:	01/2025
Interim Study Report Submissions:	10/2025
	04/2026
	10/2026
	04/2027
	10/2027
	04/2028
	10/2028
	04/2029

Interim Study Report Submissions (cont'd):	10/2029
	04/2030
	10/2030
	04/2031
	10/2031
	04/2032
	10/2032
	04/2033
	10/2033
	04/2034
	10/2034
Study Completion:	01/2035
Final Report Submission:	01/2036

4497-2 Use emerging safety data from ongoing studies and published literature, validate administrative claim codes for intracerebral hemorrhage in patients with Alzheimer's disease. The outcome of intracerebral hemorrhage should distinguish between amyloid related imaging abnormalities-hemosiderin deposition (ARIA-H) and cerebral hemorrhage greater than 1 cm. Secondary outcomes of interest include ARIA-edema (ARIA-E) and ARIA-H, seizures, anaphylaxis, and death. For secondary outcomes not well validated, develop algorithms and/or computable phenotypes using data leveraged from PMR 4497-1 and other sources for the outcomes of interest. Describe an approach to identifying an appropriate comparator group with Alzheimer's disease untreated with lecanemab-irmb. Obtain FDA agreement with the outcome algorithm specifications and comparator population prior to proceeding to conducting the retrospective cohort study. Based upon validated algorithms agreed to by the Sponsor and FDA, conduct a comparative retrospective cohort study using claims data with available medical chart review as needed or electronic health record data to assess clinical safety outcomes in a broad population of Alzheimer's disease patients treated with lecanemab-irmb.

The timetable you submitted on July 5, 2023, states that you will conduct this study according to the following schedule:

Draft Protocol Submission (Algorithm Development):	07/2024
Interim Report Submission (Algorithm Development Final Protocol):	11/2025
Interim Report Submission (Outcome Algorithm):	05/2027
Interim Report Submission (Draft Retrospective Cohort Study Protocol):	02/2028
Final Study Protocol Submission (Retrospective Cohort):	12/2028

Study Completion (Retrospective Cohort):	12/2029
Final Report Submission:	12/2030

FDA considers the term *final* to mean that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial.[1]

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess a known serious risk of amyloid related imaging abnormalities in patients who are homozygous for ApoE ε4.

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

4497-3 Further characterize the safety of treatment with lecanemab-irmb in patients who are homozygous for ApoE ε4. We would accept information on this risk from a randomized, clinical trial in participants with early preclinical Alzheimer's disease and intermediate amyloid (i.e., AHEAD 3-45 Study). Ensure that approximately 15% of the population, distributed equally among lecanemab-irmb and control, is homozygous for ApoE ε4.

The timetable you submitted on July 6, 2023, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	07/2023
Final Protocol Submission:	05/2024
Trial Completion:	08/2029
Final Report Submission:	02/2030

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

REQUIRED POSTMARKETING CORRESPONDENCE UNDER 505(o)

Submit the protocol(s) to your IND 105081, with a cross-reference letter to this BLA. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final report(s) to your BLA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **"Required Postmarketing Protocol Under 505(o)"**, **"Required**

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

Postmarketing Final Report Under 505(o)”, **“Required Postmarketing Correspondence Under 505(o)”**.

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

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

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

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

We remind you of your postmarketing commitments:

4497-4 Conduct adequate analytical validation testing to establish and support labeling of an FDA cleared or approved in vitro diagnostic device to accurately and reliably detect ApoE e4 alleles that is safe and effective for identifying patients at increased risk of ARIA if treated with Leqembi. The results of the validation studies are intended to inform product labeling.

The timetable you submitted on July 5, 2023, states that you will conduct this study according to the following schedule:

Final Report Submission: 07/2025

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}

Sally Yasuda, MS, PharmD
Deputy Director for Safety
Division of Neurology 1
Office of Neuroscience
Office of New Drugs
Center for Drug Evaluation and Research

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

/s/

SALLY U YASUDA
08/22/2023 03:16:01 PM

BLA 761269/S-001

SUPPLEMENT APPROVAL
FULFILLMENT OF POSTMARKETING REQUIREMENT
NEW POSTMARKETING REQUIREMENT
NEW POSTMARKETING COMMITMENT

Eisai Inc.
Attention: Stacie P. O'Sullivan
Director, Global Regulatory Strategy
200 Metro Boulevard
Nutley, NJ 07110

Dear Ms. O'Sullivan:

Please refer to your supplemental biologics license application (sBLA), dated and received on January 6, 2023, and your amendments, submitted under section 351(a) of the Public Health Service Act for Leqembi (lecanemab-irmb) injection.

This Prior Approval sBLA provides the final clinical study report for Study BAN2401-G000-301 (Study 301) to address PMR 4384-1. Study 301 was conducted to verify the clinical benefit of Leqembi (lecanemab-irmb) as required under 21 CFR 601 Subpart E for Accelerated Approval of Biological Products for Serious or Life-Threatening Illnesses.

APPROVAL & LABELING

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

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, via the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format, as described at FDA.gov,[1] that is identical to the enclosed labeling (text for the Prescribing Information and Medication Guide) and include the labeling changes proposed in any pending "Changes Being Effected" (CBE) supplements.

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*.[2]

The SPL will be accessible via publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this BLA, including pending "Changes Being Effected" (CBE) supplements, for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 601.12(f)] in Microsoft Word format that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission(s), provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

SUBPART E FULFILLED

We approved this BLA under the regulations at 21 CFR 601 Subpart E for Accelerated Approval of Biological Products for Serious or Life-Threatening Illnesses. Approval of this supplement fulfills your commitments made under 21 CFR 601.41.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

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

FULFILLMENT OF POSTMARKETING REQUIREMENT

We have received your submission dated January 6, 2023, containing the final report for the following postmarketing requirement listed in the January 6, 2023, accelerated approval letter for BLA 761269.

[2] 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.

4384-1: In order to verify the clinical benefit of lecanemab-irmb, conduct a randomized, controlled trial to evaluate the efficacy of lecanemab-irmb compared to an appropriate control for the treatment of Alzheimer's disease. The trial should be of sufficient duration to observe changes on an acceptable endpoint in the patient population enrolled in the trial.

We have reviewed your submission and conclude that the above requirement was fulfilled.

POSTMARKETING REQUIREMENTS UNDER 505(o)

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

Since Leqembi was approved on January 6, 2023, we have become aware of clinical trial data showing an increased risk of symptomatic, serious, and severe radiographic amyloid related imaging abnormalities (ARIA) in ApoE ε4 homozygotes who are treated with Leqembi compared to heterozygotes and noncarriers. We have also become aware of clinical trial data showing intracerebral hemorrhage greater than 1 cm in patients taking Leqembi who have risk factors for intracerebral hemorrhage that include findings on neuroimaging suggestive of cerebral amyloid angiopathy (CAA) and use of anticoagulants. We consider this information to be "new safety information" as defined in section 505-1(b)(3) of the FDCA.

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

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

4384-5 Conduct a registry-based, prospective, observational study to evaluate clinical safety outcomes among Alzheimer's disease patients treated with lecanemab-irmb, using, for example, the Alzheimer's Network for Treatment and Diagnostics (ALZ-NET) registry, including patients who are ApoE ε4 homozygotes, and/or exposed to antithrombotics, and/or have a diagnosis of, or imaging findings consistent with a high risk for, cerebral amyloid angiopathy. The primary clinical safety outcomes should include amyloid related imaging abnormalities (ARIA)-edema (ARIA-E), and ARIA-hemosiderin deposition (ARIA-H) and any associated clinical symptoms, and intracerebral hemorrhage >1 cm in size. Additional outcomes of interest should also include seizures, anaphylaxis, and death. Baseline

characterization of the registry population should include demographic data, diagnosis and stage of disease, ApoE genotype, baseline MRI findings (e.g., microhemorrhages, evidence of cerebral amyloid angiography or other imaging findings consistent with high risk of cerebral amyloid angiography, etc.), other biomarkers that are potential predictors of disease course or adverse outcomes, and prior medications including prior Alzheimer's disease (AD) therapy and antithrombotic therapy. The registry should also collect information on concomitant medications (e.g., antiplatelet and antithrombotic drugs, other AD treatments). When available, the study should provide a comparison of safety outcomes to estimated background rates in an appropriate comparator population.

The timetable you submitted on July 5, 2023, states that you will conduct this study according to the following schedule:

Draft Protocol Submission: 03/2024
Final Protocol Submission: 01/2025
Interim Study Report Submission: 10/2025
04/2026
10/2026
04/2027
10/2027
04/2028
10/2028
04/2029
10/2029
04/2030
10/2030
04/2031
10/2031
04/2032
10/2032
04/2033
10/2033
04/2034
10/2034
Study Completion: 01/2035
Final Report Submission: 01/2036

4384-6 Use emerging safety data from ongoing studies and published literature, validate administrative claim codes for intracerebral hemorrhage in patients with Alzheimer's disease. The outcome of intracerebral hemorrhage should distinguish between amyloid related imaging abnormalities-hemosiderin deposition (ARIA-H) and cerebral hemorrhage greater than 1 cm. Secondary outcomes of interest include ARIA-edema (ARIA-E) and ARIA-H, seizures, anaphylaxis, and death. For secondary

outcomes not well validated, develop algorithms and/or computable phenotypes using data leveraged from PMR 4384-5 and other sources for the outcomes of interest. Describe an approach to identifying an appropriate comparator group with Alzheimer's disease untreated with lecanemab-irmb. Obtain FDA agreement with the outcome algorithm specifications and comparator population prior to proceeding to conducting the retrospective cohort study. Based upon validated algorithms agreed to by the Sponsor and FDA, conduct a comparative retrospective cohort study using claims data with available medical chart review as needed or electronic health record data to assess clinical safety outcomes in a broad population of Alzheimer's disease patients treated with lecanemab-irmb.

The timetable you submitted on July 5, 2023, states that you will conduct this study according to the following schedule:

Draft Protocol for Algorithm Development Submission:	07/2024
Final Protocol for Algorithm Development Submission:	11/2025
Outcome Algorithm Submission:	05/2027
Draft Retrospective Cohort Study Protocol Submission:	02/2028
Final Retrospective Cohort Study Protocol Submission:	12/2028
Retrospective Cohort Study Completion:	12/2029
Final Report Submission:	12/2030

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

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess a known serious risk of amyloid related imaging abnormalities in patients who are homozygous for ApoE ε4.

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

4384-7 Further characterize the safety of treatment with lecanemab-irmb in patients who are homozygous for ApoE ε4. We would accept information on this risk from a randomized, clinical trial in participants with early preclinical Alzheimer's disease and intermediate amyloid (i.e., AHEAD 3-

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

45 Study). Ensure that approximately 15% of the population, distributed equally among lecanemab-irmb and control, is homozygous for ApoE ε4.

The timetable you submitted on July 6, 2023, states that you will conduct this study according to the following schedule:

Draft Protocol Submission: 07/2023
Final Protocol Submission: 05/2024
Trial Completion: 08/2029
Final Report Submission: 02/2030

FDA considers the term *final* to mean that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial.[4]

REQUIRED POSTMARKETING CORRESPONDENCE UNDER 505(o)

Submit the protocol(s) to your IND 105081, with a cross-reference letter to this BLA. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final report(s) to your BLA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **"Required Postmarketing Protocol Under 505(o)", "Required Postmarketing Final Report Under 505(o)", "Required Postmarketing Correspondence Under 505(o)"**.

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

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

FDA will consider the submission of your annual report under section 506B and 21 CFR 601.70 to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 601.70. We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to

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

investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

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

We remind you of your postmarketing commitments:

4384-8	Conduct adequate analytical validation testing to establish and support labeling of an FDA cleared or approved in vitro diagnostic device to accurately and reliably detect ApoE e4 alleles that is safe and effective for identifying patients at increased risk of ARIA if treated with Leqembi. The results of the validation studies are intended to inform product labeling.

The timetable you submitted on July 5, 2023, states that you will conduct this study according to the following schedule:

Final Report Submission: 07/2025

REQUESTED PHARMACOVIGILANCE

We request expedited reporting of any deaths in ongoing studies and expedited reporting of events of cerebral hemorrhage greater than 1 centimeter in size in ongoing studies or in the postmarketing setting.

We request that you perform postmarketing pharmacovigilance to characterize the risk of ARIA and the monitoring for ARIA associated with the use of Leqembi. Please provide biannual reports of ARIA-E and ARIA-H (specifying microhemorrhage or superficial siderosis), along with any incident cerebral hemorrhage greater than 1 centimeter in size. Provide a synthesized summary and analysis, including incidence of clinical trial cases, postmarketing cases, and total cases. Include an evaluation of central nervous system hemorrhage in patients with pre-existing risk factors for bleeding, including concomitant medications that could increase the risk for bleeding. Include an analysis that addresses the monitoring recommendations provided for in the prescribing information. The summary should provide an analysis for all subjects and a separate analysis for those in the United States and for those in the rest of the world. For each case, provide line listings that include:

- Case ID
- Whether the case was a clinical trial case, postmarketing spontaneous report, or postmarketing from a registry
- Age
- Alzheimer's disease stage
- Patient characteristics, including ApoE ε4 genotype if available

- Country where patient is treated
- Concomitant medications
- Time from first Leqembi dose to ARIA
- Listing of dates of Leqembi dosing
- Dates of MRI, including baseline MRI
- Description of MRI findings, including baseline MRI
- Whether patient was symptomatic and if so, list symptoms
- Whether initial finding was symptom or MRI
- Patient outcome (e.g., death, permanent disability, resolved)
- Date of resolution of MRI and of symptoms
- Whether the patient was hospitalized
- Whether and what treatment was received for ARIA
- Whether Leqembi was held, and date that Leqembi dosing resumed
- Whether Leqembi was discontinued
- Specialty of the prescribing physician (e.g., neurologist, psychiatrist, internist)

We request that you perform postmarketing pharmacovigilance and provide biannual reports to identify and analyze cases of central nervous system vasculitis that occur after use of Leqembi.

We request that you perform postmarketing pharmacovigilance to characterize the risk of infusion reactions associated with the use of Leqembi. Please provide biannual reports of serious infusion reactions, including line listings of the cases, FAERS reports, and a synthesized summary and analysis including incidence of clinical trial cases, postmarketing cases, and total cases.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. For information about submitting promotional materials, see the final guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format—Promotional Labeling and Advertising Materials for Human Prescription Drugs.*[5]

As required under 21 CFR 601.12(f)(4), you must submit final promotional materials, and the Prescribing Information, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at FDA.gov.[6] Information and Instructions for completing the form can be found at FDA.gov.[7]

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

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved BLA (in 21 CFR 600.80 and in 21 CFR 600.81).

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}

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

ENCLOSURE(S):

- Content of Labeling
  - Prescribing Information
  - Medication Guide

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

/s/

TERESA J BURACCHIO
07/06/2023 03:54:16 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761269Orig1s001

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use LEQEMBI® safely and effectively. See full prescribing information for LEQEMBI®.

LEQEMBI® (lecanemab-irmb) injection, for intravenous use
Initial U.S. Approval: 2023

WARNING: AMYLOID RELATED IMAGING ABNORMALITIES
See full prescribing information for complete boxed warning.

Monoclonal antibodies directed against aggregated forms of beta amyloid, including LEQEMBI, can cause amyloid related imaging abnormalities (ARIA), characterized as ARIA with edema (ARIA-E) and ARIA with hemosiderin deposition (ARIA-H). ARIA is usually asymptomatic, although rarely serious and life-threatening events can occur. Serious intracerebral hemorrhage greater than 1 cm have occurred in patients treated with this class of medications. (5.1, 6.1)

ApoE ε4 Homozygotes

Patients treated with this class of medications, including LEQEMBI, who are ApoE ε4 homozygotes have a higher incidence of ARIA, including symptomatic and serious ARIA, compared to heterozygotes and noncarriers. Testing for ApoE ε4 status should be performed prior to initiation of treatment to inform the risk of developing ARIA. Prior to testing, prescribers should discuss with patients the risk of ARIA across genotypes and the implications of genetic testing results. (5.1)

Consider the benefit of LEQEMBI for the treatment of Alzheimer's disease and potential risk of serious adverse events associated with ARIA when deciding to initiate treatment with LEQEMBI. (5.1, 14)

---------- RECENT MAJOR CHANGES ----------

Boxed Warning	7/2023
Indications and Usage (1)	7/2023
Dosage and Administration (2.3)	7/2023
Contraindications (4)	7/2023
Warnings and Precautions (5.1, 5.2, 5.3)	7/2023

---------- INDICATIONS AND USAGE ----------

LEQEMBI is indicated for the treatment of Alzheimer's disease. Treatment with LEQEMBI should be initiated in patients with mild cognitive impairment or mild dementia stage of disease, the population in which treatment was initiated in clinical trials. (1)

---------- DOSAGE AND ADMINISTRATION ----------

- Confirm the presence of amyloid beta pathology prior to initiating treatment. (2.1)
- The recommended dosage is 10 mg/kg that must be diluted then administered as an intravenous infusion over approximately one hour, once every two weeks. (2.2)
- Obtain a recent baseline brain MRI prior to initiating treatment. (2.3, 5.1)
- Obtain an MRI prior to the 5th, 7th, and 14th infusions. If radiographically observed ARIA occurs, treatment recommendations are based on type, severity, and presence of symptoms. (2.3, 5.1)
- Dilution in 250 mL of 0.9% Sodium Chloride Injection, USP, is required prior to administration. (2.4)
- Administer as an intravenous infusion over approximately one hour via a terminal low-protein binding 0.2 micron in-line filter. (2.5)

---------- DOSAGE FORMS AND STRENGTHS ----------

Injection:

- 500 mg/5 mL (100 mg/mL) solution in a single-dose vial (3)
- 200 mg/2 mL (100 mg/mL) solution in a single-dose vial (3)

---------- CONTRAINDICATIONS ----------

LEQEMBI is contraindicated in patients with serious hypersensitivity to lecanemab-irmb or to any of the excipients of LEQEMBI. (4)

---------- WARNINGS AND PRECAUTIONS ----------

- Amyloid Related Imaging Abnormalities (ARIA): Enhanced clinical vigilance for ARIA is recommended during the first 14 weeks of treatment with LEQEMBI. Risk of ARIA, including symptomatic ARIA, was increased in apolipoprotein E ε4 homozygotes compared to heterozygotes and noncarriers. If a patient experiences symptoms suggestive of ARIA, clinical evaluation should be performed, including MRI scanning if indicated. (2.3, 5.1)
- Infusion-Related Reactions: The infusion rate may be reduced, or the infusion may be discontinued, and appropriate therapy administered as clinically indicated. Consider pre-medication at subsequent dosing with antihistamines, non-steroidal anti-inflammatory drugs, or corticosteroids. (5.2)

---------- ADVERSE REACTIONS ----------

Most common adverse reactions (at approximately 10% and higher incidence compared to placebo): infusion-related reactions, amyloid related imaging abnormality-microhemorrhages, amyloid related imaging abnormality-edema/effusion, and headache. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Eisai Inc. at 1-888-274-2378 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 7/2023

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: AMYLOID RELATED IMAGING ABNORMALITIES

Monoclonal antibodies directed against aggregated forms of beta amyloid, including LEQEMBI, can cause amyloid related imaging abnormalities (ARIA), characterized as ARIA with edema (ARIA-E) and ARIA with hemosiderin deposition (ARIA-H). Incidence and timing of ARIA vary among treatments. ARIA usually occurs early in treatment and is usually asymptomatic, although serious and life-threatening events rarely can occur. Serious intracerebral hemorrhages, some of which have been fatal, have been observed in patients treated with this class of medications *[see Warnings and Precautions (5.1), Adverse Reactions (6.1)]*.

ApoE ε4 Homozygotes

Patients who are apolipoprotein E ε4 (ApoE ε4) homozygotes (approximately 15% of Alzheimer's disease patients) treated with this class of medications, including LEQEMBI, have a higher incidence of ARIA, including symptomatic, serious, and severe radiographic ARIA, compared to heterozygotes and noncarriers. Testing for ApoE ε4 status should be performed prior to initiation of treatment to inform the risk of developing ARIA. Prior to testing, prescribers should discuss with patients the risk of ARIA across genotypes and the implications of genetic testing results. Prescribers should inform patients that if genotype testing is not performed they can still be treated with LEQEMBI; however, it cannot be determined if they are ApoE ε4 homozygotes and at higher risk for ARIA *[see Warnings and Precautions (5.1)]*.

Consider the benefit of LEQEMBI for the treatment of Alzheimer's disease and potential risk of serious adverse events associated with ARIA when deciding to initiate treatment with LEQEMBI *[see Warnings and Precautions (5.1) and Clinical Studies (14)]*.

1 INDICATIONS AND USAGE

LEQEMBI is indicated for the treatment of Alzheimer's disease. Treatment with LEQEMBI should be initiated in patients with mild cognitive impairment or mild dementia stage of disease, the population in which treatment was initiated in clinical trials.

2 DOSAGE AND ADMINISTRATION

2.1 Patient Selection

Confirm the presence of amyloid beta pathology prior to initiating treatment *[see Clinical Pharmacology (12.1)]*.

2.2 Dosing Instructions

The recommended dosage of LEQEMBI is 10 mg/kg that must be diluted then administered as an intravenous infusion over approximately one hour, once every two weeks.

If an infusion is missed, administer the next dose as soon as possible.

2.3 Monitoring and Dosing Interruption for Amyloid Related Imaging Abnormalities

LEQEMBI can cause amyloid related imaging abnormalities -edema (ARIA-E) and -hemosiderin deposition (ARIA-H) *[see Warnings and Precautions (5.1)]*.

Monitoring for ARIA

Obtain a recent baseline brain magnetic resonance imaging (MRI) prior to initiating treatment with LEQEMBI. Obtain an MRI prior to the 5th, 7th, and 14th infusions. If a patient experiences symptoms suggestive of ARIA, clinical evaluation should be performed, including an MRI if indicated.

Recommendations for Dosing Interruptions in Patients with ARIA

ARIA-E
The recommendations for dosing interruptions for patients with ARIA-E are provided in Table 1.

Table 1: Dosing Recommendations for Patients with ARIA-E

Clinical Symptom Severity[1]	**ARIA-E Severity on MRI[2]**		
	Mild	**Moderate**	**Severe**
Asymptomatic	May continue dosing	Suspend dosing[3]	Suspend dosing[3]
Mild	May continue dosing based on clinical judgment	Suspend dosing[3]	
Moderate or Severe	Suspend dosing[3]		

[1] Clinical Symptom Severity Categories:
Mild: discomfort noticed, but no disruption of normal daily activity.
Moderate: discomfort sufficient to reduce or affect normal daily activity.
Severe: incapacitating, with inability to work or to perform normal daily activity.
[2] See Table 3 for MRI severity *[Warnings and Precautions (5.1)]*.
[3] Suspend until MRI demonstrates radiographic resolution and symptoms, if present, resolve; consider a follow-up MRI to assess for resolution 2 to 4 months after initial identification. Resumption of dosing should be guided by clinical judgment.

ARIA-H
The recommendations for dosing interruptions for patients with ARIA-H are provided in Table 2.

Table 2: Dosing Recommendations for Patients with ARIA-H

Clinical Symptom Severity	**ARIA-H Severity on MRI[1]**		
	Mild	**Moderate**	**Severe**
Asymptomatic	May continue dosing	Suspend dosing[2]	Suspend dosing[3]
Symptomatic	Suspend dosing[2]	Suspend dosing[2]	

[1] See Table 3 for MRI severity *[Warnings and Precautions (5.1)]*.

[2] Suspend until MRI demonstrates radiographic stabilization and symptoms, if present, resolve; resumption of dosing should be guided by clinical judgment; consider a follow-up MRI to assess for stabilization 2 to 4 months after initial identification.
[3] Suspend until MRI demonstrates radiographic stabilization and symptoms, if present, resolve; use clinical judgment in considering whether to continue treatment or permanently discontinue LEQEMBI.

In patients who develop intracerebral hemorrhage greater than 1 cm in diameter during treatment with LEQEMBI, suspend dosing until MRI demonstrates radiographic stabilization and symptoms, if present, resolve. Use clinical judgment in considering whether to continue treatment after radiographic stabilization and resolution of symptoms or permanently discontinue LEQEMBI.

2.4 Dilution Instructions

- Prior to administration, LEQEMBI must be diluted in 250 mL of 0.9% Sodium Chloride Injection, USP.
- Use aseptic technique when preparing the LEQEMBI diluted solution for intravenous infusion.
- Calculate the dose (mg), the total volume (mL) of LEQEMBI solution required, and the number of vials needed based on the patient's actual body weight and the recommended dose of 10 mg/kg. Each vial contains a LEQEMBI concentration of 100 mg/mL.
- Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Check that the LEQEMBI solution is clear to opalescent and colorless to pale yellow. Do not use if opaque particles, discoloration, or other foreign particles are present.
- Remove the flip-off cap from the vial. Insert the sterile syringe needle into the vial through the center of the rubber stopper.
- Withdraw the required volume of LEQEMBI from the vial(s) and add to an infusion bag containing 250 mL of 0.9% Sodium Chloride Injection, USP.
- Each vial is for one-time use only. Discard any unused portion.
- Gently invert the infusion bag containing the LEQEMBI diluted solution to mix completely. Do not shake.
- After dilution, immediate use is recommended *[see Description (11)]*. If not administered immediately, store LEQEMBI refrigerated at 2°C to 8°C (36°F to 46°F) for up to 4 hours, or at room temperature up to 30°C (86°F) for up to 4 hours. Do not freeze.

2.5 Administration Instructions

- Visually inspect the LEQEMBI diluted solution for particles or discoloration prior to administration. Do not use if it is discolored, or opaque or foreign particles are seen.
- Prior to infusion, allow the LEQEMBI diluted solution to warm to room temperature.
- Infuse the entire volume of the LEQEMBI diluted solution intravenously over approximately one hour through an intravenous line containing a terminal low-protein binding 0.2 micron in-line filter. Flush infusion line to ensure all LEQEMBI is administered.
- Monitor for any signs or symptoms of an infusion-related reaction. The infusion rate may be reduced, or the infusion may be discontinued, and appropriate therapy administered as clinically indicated. Consider pre-medication at subsequent dosing with antihistamines, non-steroidal anti-inflammatory drugs, or corticosteroids *[see Warnings and Precautions (5.2)]*.

3 DOSAGE FORMS AND STRENGTHS

LEQEMBI is a clear to opalescent and colorless to pale yellow solution, available as:

- Injection: 500 mg/5 mL (100 mg/mL) in a single-dose vial
- Injection: 200 mg/2 mL (100 mg/mL) in a single-dose vial

4 CONTRAINDICATIONS

LEQEMBI is contraindicated in patients with serious hypersensitivity to lecanemab-irmb or to any of the excipients of LEQEMBI. Reactions have included angioedema and anaphylaxis *[see Warnings and Precautions (5.2)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Amyloid Related Imaging Abnormalities

Monoclonal antibodies directed against aggregated forms of beta amyloid, including LEQEMBI, can cause amyloid related imaging abnormalities (ARIA), characterized as ARIA with edema (ARIA-E), which can be observed on MRI as brain edema or sulcal effusions, and ARIA with hemosiderin deposition (ARIA-H), which includes microhemorrhage and superficial siderosis. ARIA can occur spontaneously in patients with Alzheimer's disease. ARIA-H associated with monoclonal antibodies directed against aggregated forms of beta amyloid generally occurs in association with an occurrence of ARIA-E. ARIA-H of any cause and ARIA-E can occur together.

ARIA usually occurs early in treatment and is usually asymptomatic, although serious and life-threatening events, including seizure and status epilepticus, rarely can occur. When present, reported symptoms associated with ARIA may include headache, confusion, visual changes, dizziness, nausea, and gait difficulty. Focal neurologic deficits may also occur. Symptoms associated with ARIA usually resolve over time. The risk of ARIA, including symptomatic and serious ARIA, is increased in apolipoprotein E ε4 (ApoE ε4) homozygotes. In addition to ARIA, intracerebral hemorrhages greater than 1 cm in diameter have occurred in patients treated with LEQEMBI.

Consider the benefit of LEQEMBI for the treatment of Alzheimer's disease and potential risk of serious adverse events associated with ARIA when deciding to initiate treatment with LEQEMBI.

Incidence of ARIA

Symptomatic ARIA occurred in 3% (29/898) of patients treated with LEQEMBI in Study 2 *[see Clinical Studies (14)]*. Serious symptoms associated with ARIA were reported in 0.7% (6/898) of patients treated with LEQEMBI. Clinical symptoms associated with ARIA resolved in 79% (23/29) of patients during the period of observation. Similar findings were observed in Study 1.

Including asymptomatic radiographic events, ARIA was observed in 21% (191/898) of patients treated with LEQEMBI, compared to 9% (84/897) of patients on placebo in Study 2.

ARIA-E was observed in 13% (113/898) of patients treated with LEQEMBI compared with 2% (15/897) of patients on placebo. ARIA-H was observed in 17% (152/898) of patients treated with LEQEMBI compared

with 9% (80/897) of patients on placebo. There was no increase in isolated ARIA-H (i.e., ARIA-H in patients who did not also experience ARIA-E) for LEQEMBI compared to placebo.

ApoE ε4 Carrier Status and Risk of ARIA

Approximately 15% of Alzheimer's disease patients are ApoE ε4 homozygotes. In Study 2, 16% (141/898) of patients in the LEQEMBI arm were ApoE ε4 homozygotes, 53% (479/898) were heterozygotes, and 31% (278/898) were noncarriers. The incidence of ARIA was higher in ApoE ε4 homozygotes (45% on LEQEMBI vs. 22% on placebo) than in heterozygotes (19% on LEQEMBI vs 9% on placebo) and noncarriers (13% on LEQEMBI vs 4% on placebo). Among patients treated with LEQEMBI, symptomatic ARIA-E occurred in 9% of ApoE ε4 homozygotes compared with 2% of heterozygotes and 1% noncarriers. Serious events of ARIA occurred in 3% of ApoE ε4 homozygotes, and approximately 1% of heterozygotes and noncarriers. The recommendations on management of ARIA do not differ between ApoE ε4 carriers and noncarriers *[see Dosage and Administration (2.3)]*. Testing for ApoE ε4 status should be performed prior to initiation of treatment to inform the risk of developing ARIA. Prior to testing, prescribers should discuss with patients the risk of ARIA across genotypes and the implications of genetic testing results. Prescribers should inform patients that if genotype testing is not performed they can still be treated with LEQEMBI; however, it cannot be determined if they are ApoE ε4 homozygotes and at higher risk for ARIA. An FDA-authorized test for the detection of ApoE ε4 alleles to identify patients at risk of ARIA if treated with LEQEMBI is not currently available. Currently available tests used to identify ApoE ε4 alleles may vary in accuracy and design.

Radiographic Findings

The radiographic severity of ARIA associated with LEQEMBI was classified by the criteria shown in Table 3.

Table 3: ARIA MRI Classification Criteria

ARIA Type	**Radiographic Severity**		
	Mild	**Moderate**	**Severe**
ARIA-E	FLAIR hyperintensity confined to sulcus and/or cortex/subcortex white matter in one location <5 cm	FLAIR hyperintensity 5 to 10 cm in single greatest dimension, or more than 1 site of involvement, each measuring <10 cm	FLAIR hyperintensity >10 cm with associated gyral swelling and sulcal effacement. One or more separate/ independent sites of involvement may be noted.
ARIA-H microhemorrhage	≤ 4 new incident microhemorrhages	5 to 9 new incident microhemorrhages	10 or more new incident microhemorrhages
ARIA-H superficial siderosis	1 focal area of superficial siderosis	2 focal areas of superficial siderosis	> 2 areas of superficial siderosis

The majority of ARIA-E radiographic events occurred early in treatment (within the first 7 doses), although ARIA can occur at any time and patients can have more than 1 episode. The maximum radiographic severity of ARIA-E in patients treated with LEQEMBI was mild in 4% (37/898) of patients, moderate in 7% (66/898) of

patients, and severe in 1% (9/898) of patients. Resolution on MRI occurred in 52% of ARIA-E patients by 12 weeks, 81% by 17 weeks, and 100% overall after detection. The maximum radiographic severity of ARIA-H microhemorrhage in patients treated with LEQEMBI was mild in 9% (79/898), moderate in 2% (19/898), and severe in 3% (28/898) of patients; superficial siderosis was mild in 4% (38/898), moderate in 1% (8/898), and severe in 0.4% (4/898). Among patients treated with LEQEMBI, the rate of severe radiographic ARIA-E was highest in ApoE ε4 homozygotes 5% (7/141), compared to heterozygotes 0.4% (2/479) or noncarriers 0% (0/278). Among patients treated with LEQEMBI, the rate of severe radiographic ARIA-H was highest in ApoE ε4 homozygotes 13.5% (19/141), compared to heterozygotes 2.1% (10/479) or noncarriers 1.1% (3/278).

Intracerebral Hemorrhage

Intracerebral hemorrhage greater than 1 cm in diameter was reported in 0.7% (6/898) of patients in Study 2 after treatment with LEQEMBI compared to 0.1% (1/897) on placebo. Fatal events of intracerebral hemorrhage in patients taking LEQEMBI have been observed.

Concomitant Antithrombotic Medication

In Study 2, baseline use of antithrombotic medication (aspirin, other antiplatelets, or anticoagulants) was allowed if the patient was on a stable dose. The majority of exposures to antithrombotic medications were to aspirin. Antithrombotic medications did not increase the risk of ARIA with LEQEMBI. The incidence of intracerebral hemorrhage was 0.9% (3/328 patients) in patients taking LEQEMBI with a concomitant antithrombotic medication at the time of the event compared to 0.6% (3/545 patients) in those who did not receive an antithrombotic. Patients taking LEQEMBI with an anticoagulant alone or combined with an antiplatelet medication or aspirin had an incidence of intracerebral hemorrhage of 2.5% (2/79 patients) compared to none in patients who received placebo.

Because intracerebral hemorrhages greater than 1 cm in diameter have been observed in patients taking LEQEMBI, additional caution should be exercised when considering the administration of anticoagulants or a thrombolytic agent (e.g., tissue plasminogen activator) to a patient already being treated with LEQEMBI.

Other Risk Factors for Intracerebral Hemorrhage

Patients were excluded from enrollment in Study 2 for findings on neuroimaging that indicated an increased risk for intracerebral hemorrhage. These included findings suggestive of cerebral amyloid angiopathy (prior cerebral hemorrhage greater than 1 cm in greatest diameter, more than 4 microhemorrhages, superficial siderosis, vasogenic edema) or other lesions (aneurysm, vascular malformation) that could potentially increase the risk of intracerebral hemorrhage.

The presence of an ApoE ε4 allele is also associated with cerebral amyloid angiopathy, which has an increased risk for intracerebral hemorrhage.

Caution should be exercised when considering the use of LEQEMBI in patients with factors that indicate an increased risk for intracerebral hemorrhage and in particular for patients who need to be on anticoagulant therapy.

Monitoring and Dose Management Guidelines

Recommendations for dosing in patients with ARIA-E depend on clinical symptoms and radiographic severity *[see Dosage and Administration (2.3)]*. Recommendations for dosing in patients with ARIA-H depend on the

type of ARIA-H and radiographic severity *[see Dosage and Administration (2.3)]*. Use clinical judgment in considering whether to continue dosing in patients with recurrent ARIA-E.

Baseline brain MRI and periodic monitoring with MRI are recommended *[see Dosage and Administration (2.3)]*. Enhanced clinical vigilance for ARIA is recommended during the first 14 weeks of treatment with LEQEMBI. If a patient experiences symptoms suggestive of ARIA, clinical evaluation should be performed, including MRI if indicated. If ARIA is observed on MRI, careful clinical evaluation should be performed prior to continuing treatment.

There is no experience in patients who continued dosing through symptomatic ARIA-E, or through asymptomatic but radiographically severe ARIA-E. There is limited experience in patients who continued dosing through asymptomatic but radiographically mild to moderate ARIA-E. There are limited data in dosing patients who experienced recurrent ARIA-E.

The Alzheimer's Network for Treatment and Diagnostics (ALZ-NET) is a voluntary provider-enrolled patient registry that collects information on treatments for Alzheimer's disease, including LEQEMBI. Providers may obtain information about the registry at www.alz-net.org or contact alz-net@acr.org.

5.2 Hypersensitivity Reactions

Hypersensitivity reactions, including angioedema, bronchospasm, and anaphylaxis, have occurred in patients who were treated with LEQEMBI. Promptly discontinue the infusion upon the first observation of any signs or symptoms consistent with a hypersensitivity reaction, and initiate appropriate therapy. LEQEMBI is contraindicated in patients with a history of serious hypersensitivity to lecanemab-irmb or to any of the excipients of LEQEMBI.

5.3 Infusion-Related Reactions

In Study 2, infusion-related reactions were observed in 26% (237/898) of patients treated with LEQEMBI compared to 7% (66/897) of patients on placebo; and the majority (75%, 178/237) occurred with the first infusion. Infusion-related reactions were mostly mild (69%) or moderate (28%) in severity. Infusion-related reactions resulted in discontinuations in 1% (12/898) of patients treated with LEQEMBI. Symptoms of infusion-related reactions include fever and flu-like symptoms (chills, generalized aches, feeling shaky, and joint pain), nausea, vomiting, hypotension, hypertension, and oxygen desaturation.

After the first infusion in Study 1, 38% of patients treated with LEQEMBI had transient decreased lymphocyte counts to less than 0.9 $x10^9$/L compared to 2% in patients on placebo, and 22% of patients treated with LEQEMBI had transient increased neutrophil counts to greater 7.9 $x10^9$/L compared to 1% of patients on placebo. Lymphocyte and neutrophil counts were not obtained after the first infusion in Study 2.

In the event of an infusion-related reaction, the infusion rate may be reduced, or the infusion may be discontinued, and appropriate therapy initiated as clinically indicated. Prophylactic treatment with antihistamines, acetaminophen, nonsteroidal anti-inflammatory drugs, or corticosteroids prior to future infusions may be considered.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Amyloid Related Imaging Abnormalities *[see Warnings and Precautions (5.1)]*
- Hypersensitivity Reactions *[see Warnings and Precautions (5.2)]*
- Infusion-Related Reactions *[see Warnings and Precautions (5.3)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety of LEQEMBI has been evaluated in 2090 patients who received at least one dose of LEQEMBI. In Studies 1 and 2 in patients with Alzheimer's disease, 1059 patients received LEQEMBI 10 mg/kg every two weeks *[see Clinical Studies (14)]*. Of these 1059 patients, 50% were female, 79% were White, 15% were Asian, 12% were of Hispanic or Latino ethnicity, and 2% were Black. The mean age at study entry was 72 years (range from 50 to 90 years).

In the combined double-blind, placebo-controlled period and long-term extension period of Studies 1 and 2, 1604 patients received LEQEMBI for at least 6 months, 1261 patients for at least 12 months, and 965 patients for 18 months.

In the double-blind, placebo-controlled period in Study 1 patients stopped study treatment because of an adverse reaction in 15% of patients treated with LEQEMBI, compared to 6% patients on placebo; in Study 2 patients stopped study treatment because of an adverse reaction in 7% of patients treated with LEQEMBI, compared to 3% patients on placebo. In Study 1, the most common adverse reaction leading to discontinuation of LEQEMBI was infusion-related reactions that led to discontinuation in 2% (4/161) of patients treated with LEQEMBI compared to 1% (2/245) of patients on placebo. In Study 2, the most common adverse reaction leading to discontinuation of LEQEMBI was ARIA-H microhemorrhages that led to discontinuation in 2% (15/898) of patients treated with LEQEMBI compared to <1% (1/897) of patients on placebo.

Table 4 shows adverse reactions that were reported in at least 5% of patients treated with LEQEMBI and at least 2% more frequently than in patients on placebo in Study 1.

Table 4: Adverse Reactions Reported in at Least 5% of Patients Treated with LEQEMBI 10 mg/kg Every Two Weeks and at least 2% Higher than Placebo in Study 1

Adverse Reaction	**LEQEMBI 10 mg/kg Every Two Weeks N=161 %**	**Placebo N=245 %**
Infusion-related reactions	20	3
Headache	14	10
ARIA-E	10	1
Cough	9	5

Adverse Reaction	LEQEMBI 10 mg/kg Every Two Weeks N=161 %	Placebo N=245 %
Diarrhea	8	5

Table 5 shows adverse reactions that were reported in at least 5% of patients treated with LEQEMBI and at least 2% more frequently than in patients on placebo in Study 2.

Table 5: Adverse Reactions Reported in at Least 5% of Patients Treated with LEQEMBI 10 mg/kg Every Two Weeks and at least 2% Higher than Placebo in Study 2

Adverse Reaction	LEQEMBI 10 mg/kg Every Two Weeks N=898 %	Placebo N=897 %
Infusion-related reactions	26	7
ARIA-H	14	8
ARIA-E	13	2
Headache	11	8
Superficial siderosis of central nervous system	6	3
Rash[1]	6	4
Nausea/Vomiting	6	4

[1] Rash includes acne, erythema, infusion site rash, injection site rash, rash, rash erythematous, rash pruritic, skin reactions, and urticaria.

Less Common Adverse Reactions

Atrial fibrillation occurred in 3% of patients treated with LEQEMBI compared to 2% in patients on placebo. In Study 1, lymphopenia or decreased lymphocyte count were reported in 4% of patients treated with LEQEMBI after the first dose, compared to less than 1% of patients on placebo *[see Warnings and Precautions (5.3)]*; lymphocytes were not measured after the first dose in Study 2.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no adequate data on LEQEMBI use in pregnant women to evaluate for a drug associated risk of major birth defects, miscarriage, or other adverse maternal or fetal outcomes. No animal studies have been conducted to assess the potential reproductive or developmental toxicity of LEQEMBI.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively. The background risk of major birth defects and miscarriage for the indicated population is unknown.

8.2 Lactation

Risk Summary

There are no data on the presence of lecanemab-irmb in human milk, the effects on the breastfed infant, or the effects of the drug on milk production. Published data from other monoclonal antibodies generally indicate low passage of monoclonal antibodies into human milk and limited systemic exposure in the breastfed infant. The effects of this limited exposure are unknown. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for LEQEMBI and any potential adverse effects on the breastfed infant from LEQEMBI or from the underlying maternal condition.

8.4 Pediatric Use

Safety and effectiveness of LEQEMBI in pediatric patients have not been established.

8.5 Geriatric Use

In Studies 1 and 2, the age of patients exposed to LEQEMBI 10 mg/kg every two weeks (n=1059) ranged from 50 to 90 years, with a mean age of 72 years; 81% were 65 years and older, and 39% were 75 years and older. No overall differences in safety or effectiveness of LEQEMBI have been observed between patients 65 years of age and older and younger adult patients.

11 DESCRIPTION

Lecanemab-irmb is a recombinant humanized immunoglobulin gamma 1 (IgG1) monoclonal antibody directed against aggregated soluble and insoluble forms of amyloid beta, and is expressed in a Chinese hamster ovary cell line. Lecanemab-irmb has an approximate molecular weight of 150 kDa.

LEQEMBI (lecanemab-irmb) injection is a preservative-free, sterile, clear to opalescent and colorless to pale yellow solution for intravenous use by infusion after dilution. LEQEMBI is supplied in single-dose vials available in concentrations of 500 mg/5 mL (100 mg/mL) or 200 mg/2 mL (100 mg/mL).

Each mL of solution contains 100 mg of lecanemab-irmb and arginine hydrochloride (42.13 mg), histidine (0.18 mg), histidine hydrochloride monohydrate (4.99 mg), polysorbate 80 (0.50 mg), and Water for Injection at an approximate pH of 5.0.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Lecanemab-irmb is a humanized immunoglobulin gamma 1 (IgG1) monoclonal antibody directed against aggregated soluble and insoluble forms of amyloid beta. The accumulation of amyloid beta plaques in the brain is a defining pathophysiological feature of Alzheimer's disease. LEQEMBI reduces amyloid beta plaques, as evaluated in Study 1 and Study 2 *[see Clinical Studies (14)]*.

12.2 Pharmacodynamics

Effect of LEQEMBI on Amyloid Beta Pathology

The effect of LEQEMBI on amyloid beta plaque levels in the brain was evaluated using Positron Emission Tomography (PET) imaging. The PET signal was quantified using the both the Standard Uptake Value Ratio (SUVR) and Centiloid scale to estimate 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).

LEQEMBI reduced amyloid beta plaque in a dose- and time-dependent manner in the dose-ranging study (Study 1) and in a time-dependent manner in single-dosing regimen study (Study 2) compared with placebo *[see Clinical Studies (14)]*.

In Study 1, treatment with LEQEMBI 10 mg/kg every two weeks reduced amyloid beta plaque levels in the brain, producing reductions in PET SUVR compared to placebo at both Weeks 53 and 79 ($p<0.0001$). The magnitude of the reduction was time- and dose-dependent.

During an off-treatment period in Study 1 (range from 9 to 59 months; mean of 24 months), SUVR and Centiloid values began to increase with a mean rate of increase of 2.6 Centiloids/year, however, treatment difference relative to placebo at the end of the double-blind, placebo-controlled period in Study 1 was maintained.

In Study 2, treatment with LEQEMBI 10 mg/kg every two weeks reduced amyloid beta plaque levels in the brain, producing reductions compared to placebo starting at Week 13 and continuing through Week 79 ($p<0.0001$).

An increase in plasma Aβ42/40 ratio (Table 6) and CSF Aβ[1-42] was observed with LEQEMBI 10 mg/kg every two weeks dosing compared to placebo.

Effect of LEQEMBI on Tau Pathophysiology

A reduction in plasma p-tau181 (Table 6), CSF p-tau181, and CSF t-tau was observed with LEQEMBI 10 mg/kg every two weeks compared to placebo.

Table 6: Effect of LEQEMBI on Plasma Aβ42/40 and Plasma p-tau181 in Study 1 and Study 2

Biomarker Endpoints	**Study 1**		**Study 2**	
	LEQEMBI 10 mg/kg Every Two Weeks	**Placebo**	**LEQEMBI 10 mg/kg Every Two Weeks**	**Placebo**
Plasma Aβ42/40[2]	N=43	N=88	N=797	N=805
Mean baseline	0.0842	0.0855	0.088	0.088
Adjusted mean change from baseline at Month 18[3]	0.0075	0.0021	0.008	0.001
Difference from placebo	0.0054 (p=0.0036)[1]		0.007 (p<0.0001)[1]	
Plasma p-tau181 (pg/mL)[2]	N=84	N=179	N=746	N=752
Mean baseline	4.6474	4.435	3.696	3.740
Adjusted mean change from baseline at Month 18[3]	-1.1127	0.0832	-0.575	0.201
Difference from placebo	-1.1960 (p<0.0001)[1]		-0.776 (p<0.0001)[1]	

N is the number of patients with baseline value.
[1] P-values were not statistically controlled for multiple comparisons.
[2] Results should be interpreted with caution due to uncertainties in bioanalysis.
[3] Month 18 represents Week 79 in Study 1 and Week 77 in Study 2

A substudy was conducted in Study 2 to evaluate the effect of LEQEMBI on neurofibrillary tangles composed of tau protein using PET imaging (^{18}F-MK6240 tracer). The PET signal was quantified using the SUVR method to estimate brain levels of tau in brain regions expected to be affected by Alzheimer's disease pathology (whole cortical gray matter, meta-temporal, frontal, cingulate, parietal, occipital, medial temporal, and temporal) in the study population compared to a brain region expected to be spared of such pathology (cerebellum). The adjusted mean change from baseline in tau PET SUVR, relative to placebo, was in favor of LEQEMBI in the medial temporal ($p<0.01$), meta temporal ($p<0.05$), and temporal ($p<0.05$) regions. No statistically significant differences were observed for the whole cortical gray matter, frontal, cingulate, parietal, or occipital regions.

Exposure-Response Relationships

Model based exposure-response analyses demonstrated that higher exposures to lecanemab-irmb were associated with greater reduction in clinical decline on Clinical Dementia Rating scale Sum of Boxes (CDR-SB) and Alzheimer Disease Assessment Scale – Cognitive Subscale 14 (ADAS-Cog14). In addition, higher exposures to lecanemab-irmb were associated with greater reduction in amyloid beta plaque. An association between reduction in amyloid beta plaque and clinical decline on CDR-SB and ADAS-Cog14 was also observed.

Higher exposures to lecanemab-irmb were also associated with greater increase in plasma Aβ42/40 ratio and greater reduction in plasma p-tau181.

12.3 Pharmacokinetics

Steady-state concentrations of lecanemab-irmb were reached after 6 weeks of 10 mg/kg administered every 2 weeks and systemic accumulation was 1.4-fold. The peak concentration (C_{max}) and area under the plasma concentration versus time curve (AUC) of lecanemab-irmb increased dose proportionally in the dose range of 0.3 to 15 mg/kg following single dose.

Distribution

The mean value (95% CI) for central volume of distribution at steady-state is 3.24 (3.18-3.30) L.

Elimination

Lecanemab-irmb is degraded by proteolytic enzymes in the same manner as endogenous IgGs. The clearance of lecanemab-irmb (95% CI) is 0.370 (0.353-0.384) L/day. The terminal half-life is 5 to 7 days.

Specific Populations

Sex, body weight, and albumin were found to impact exposure to lecanemab-irmb. However, none of these covariates were found to be clinically significant.

Patients with Renal or Hepatic Impairment

No clinical studies were conducted to evaluate the pharmacokinetics of lecanemab-irmb in patients with renal or hepatic impairment. Lecanemab-irmb is degraded by proteolytic enzymes and is not expected to undergo renal elimination or metabolism by hepatic enzymes.

12.6 Immunogenicity

The observed incidence of anti-drug antibodies is highly dependent on the sensitivity and specificity of the assay. Differences in assay methods preclude meaningful comparisons of the incidence of anti-drug antibodies in the studies described below with the incidence of anti-drug antibodies in other studies, including those of lecanemab-irmb or of other lecanemab products.

During the 18-month treatment period in Study 1, 63/154 (40.9%) of patients treated with LEQEMBI 10 mg/kg every two weeks developed anti-lecanemab-irmb antibodies. Of these patients, neutralizing anti-lecanemab-irmb antibodies were detected in 16/63 (25.4%) patients. However, the assays used to measure anti-lecanemab-irmb antibodies and neutralizing antibodies are subject to interference by serum lecanemab concentrations, possibly resulting in an underestimation of the incidence of antibody formation. Therefore, there is insufficient information to characterize the effects of anti-lecanemab-irmb antibodies on pharmacokinetics, pharmacodynamics, safety, or effectiveness of LEQEMBI.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Carcinogenicity studies have not been conducted.

Mutagenesis

Genotoxicity studies have not been conducted.

Impairment of Fertility

No studies in animals have been conducted to assess the effects of lecanemab-irmb on male or female fertility. No adverse effects on male or female reproductive organs were observed in a 39-week intravenous toxicity study in monkeys administered lecanemab-irmb weekly at doses up to 100 mg/kg. The highest dose tested was associated with plasma exposures (C_{ave}) approximately 27 times that in humans at the recommended human dose (10 mg/kg every two weeks).

14 CLINICAL STUDIES

The efficacy of LEQEMBI was evaluated in two double-blind, placebo-controlled, parallel-group, randomized studies (Study 1, NCT01767311; Study 2 NCT03887455) in patients with Alzheimer's disease (patients with confirmed presence of amyloid pathology and mild cognitive impairment [64% of patients in Study 1; 62% of patients in Study 2] or mild dementia stage of disease [36% of patients in Study 1; 38% of patients in Study 2], consistent with Stage 3 and Stage 4 Alzheimer's disease). In both studies, patients were enrolled with a Clinical Dementia Rating (CDR) global score of 0.5 or 1.0 and a Memory Box score of 0.5 or greater. All patients had a Mini-Mental State Examination (MMSE) score of ≥22 and ≤30, and had objective impairment in episodic memory as indicated by at least 1 standard deviation below age-adjusted mean in the Wechsler-Memory Scale-IV Logical Memory II (subscale) (WMS-IV LMII). Patients were enrolled with or without concomitant approved therapies (cholinesterase inhibitors and the N-methyl-D-aspartate antagonist memantine) for Alzheimer's disease. Patients in each study could enroll in an optional, long-term extension.

Study 1

In Study 1, 856 patients were randomized to receive one of 5 doses (161 of which were randomized to the recommended dosing regimen of 10 mg/kg every two weeks) of LEQEMBI or placebo (n=247). Of the total number of patients randomized, 71.4% were ApoE ε4 carriers and 28.6% were ApoE ε4 non-carriers. During the study the protocol was amended to no longer randomize ApoE ε4 carriers to the 10 mg/kg every two weeks dose arm. ApoE ε4 carriers who had been receiving LEQEMBI 10 mg/kg every two weeks for 6 months or less were discontinued from study drug. As a result, in the LEQEMBI 10 mg/kg every two weeks arm, 30.3% of patients were ApoE ε4 carriers and 69.7% were ApoE ε4 non-carriers. At baseline, the mean age of randomized patients was 71 years, with a range of 50 to 90 years. Fifty percent of patients were male and 90% were White.

In Study 1, a subgroup of 315 patients were enrolled in the amyloid PET substudy; of these, 277 were evaluated at Week 79. Results from the amyloid beta PET substudy are described in Figure 1 and Table 7. Plasma biomarkers are described in Table 5.

Figure 1: Reduction in Brain Amyloid Beta Plaque (Adjusted Mean Change from Baseline in Amyloid Beta PET Composite, SUVR and Centiloids) in Study 1

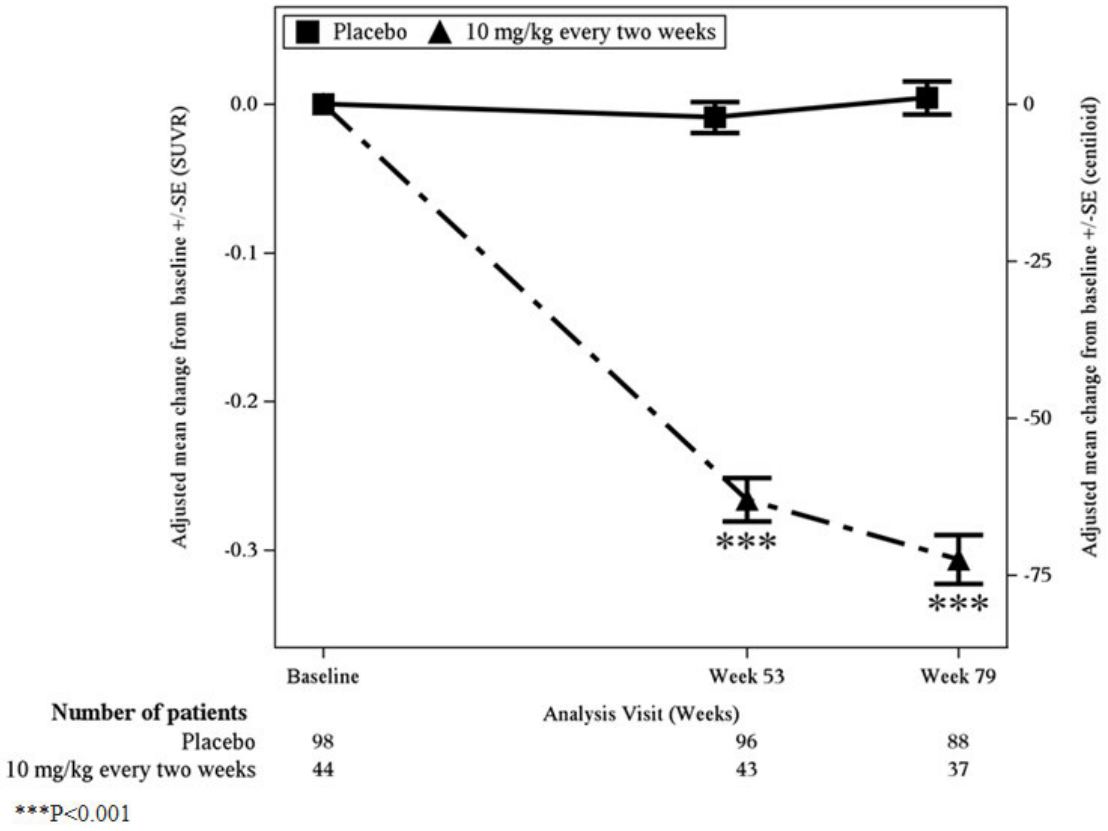


Table 7: Results for Amyloid Beta PET in Study 1

Biomarker Endpoints	**LEQEMBI 10 mg/kg Every Two Weeks**	**Placebo**
Amyloid Beta PET Composite SUVR	N=44	N=98
Mean baseline	1.373	1.402
Adjusted mean change from baseline at Week 79	-0.306	0.004
Difference from placebo	-0.310 (p<0.001) [1]	
Amyloid Beta PET Centiloid	N=44	N=98
Mean baseline	78.0	84.8
Adjusted mean change from baseline at Week 79	-72.5	1.0
Difference from placebo	-73.5 (p<0.001) [1]	

N is the number of patients with baseline value.
[1] P-values were not statistically controlled for multiple comparisons.

The primary endpoint was change from baseline on a weighted composite score consisting of selected items from the Clinical Dementia Rating scale Sum of Boxes (CDR-SB), MMSE, and Alzheimer Disease Assessment Scale – Cognitive Subscale 14 (ADAS-Cog 14) at Week 53. LEQEMBI had a 64% likelihood of 25% or greater slowing of progression on the primary endpoint relative to placebo at Week 53, which did not meet the prespecified success criterion of 80%.

Key secondary efficacy endpoints included the change from baseline in amyloid PET SUVR composite at Week 79 and change from baseline in the CDR-SB and ADAS-Cog14 at Week 79. Results for clinical assessments showed less change from baseline in CDR-SB and ADAS-Cog 14 scores at Week 79 in the LEQEMBI group than in patients on placebo (CDR-SB: -0.40 [26%], 90% CI [-0.82, 0.03]; ADAS-Cog 14: -2.31 [47%], 90% CI [-3.91, -0.72].

After the 79-week double-blind, placebo-controlled period of Study 1, patients could enroll in an open-label extension period for up to 260 weeks, which was initiated after a gap period (range 9 to 59 months; mean 24 months) off treatment.

Study 2

In Study 2, 1795 patients were enrolled and randomized 1:1 to receive LEQEMBI 10 mg/kg or placebo once every 2 weeks. Of the total number of patients randomized, 69% were ApoE ε4 carriers and 31% were ApoE ε4 non-carriers. Overall median age of patients was 72 years, with a range of 50 to 90 years. Fifty-two percent were women, and 1381 (77%) were White, 303 (17%) were Asian, and 47 (3%) were Black.

The randomization was stratified according to clinical subgroup (mild cognitive impairment or mild dementia stage of the disease); the presence or absence of concomitant approved therapies for Alzheimer's disease at baseline (cholinesterase inhibitors and the N-methyl-D-aspartate antagonist memantine); ApoE ε4 carrier status; and geographical region.

The primary efficacy outcome was change from baseline at 18 months in the CDR-SB. Key secondary endpoints included change from baseline at 18 months for the following measures: amyloid Positron Emission Tomography (PET) using Centiloids, ADAS-Cog14, and Alzheimer's Disease Cooperative Study-Activities of Daily Living Scale for Mild Cognitive Impairment (ADCS MCI-ADL).

LEQEMBI treatment met the primary endpoint and reduced clinical decline on the global cognitive and functional scale, CDR-SB, compared with placebo at 18 months (-0.45 [-27%], $p<0.0001$).

Statistically significant differences ($p<0.01$) between treatment groups were also seen in the results for ADAS-Cog14 and ADCS MCI-ADL at 18 months as presented in Table 8.

Both ApoE ε4 carriers and ApoE ε4 noncarriers showed statistically significant treatment differences for the primary endpoint and all secondary endpoints. In an exploratory subgroup analysis of ApoE ε4 homozygotes, which represented 15% of the trial population, a treatment effect was not observed with LEQEMBI treatment on the primary endpoint, CDR-SB, compared to placebo, although treatment effects that favored LEQEMBI were observed for the secondary clinical endpoints, ADAS-Cog 14 and ADCS MCI-ADL. Treatment effects on disease-relevant biomarkers (amyloid beta PET, plasma Aβ42/40 ratio, plasma p-tau 181) also favored LEQEMBI in the ApoE ε4 homozygous subgroup.

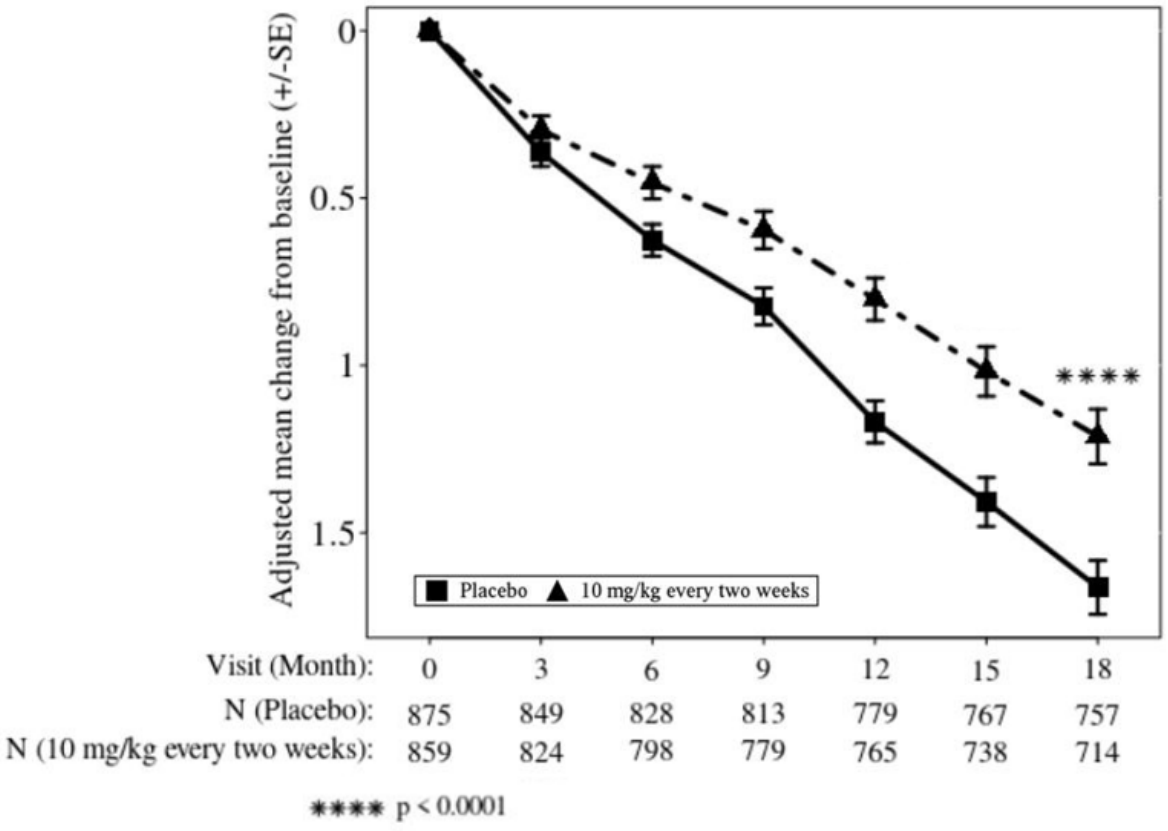
Starting at six months, across all time points, LEQEMBI treatment showed statistically significant changes in the primary and all key secondary endpoints from baseline compared to placebo; see Figure 2.

Table 8: Results for CDR-SB, ADAS-Cog14, and ADCS MCI-ADL in Study 2

Clinical Endpoints	**LEQEMBI 10 mg/kg Every Two Weeks**	**Placebo**
CDR-SB	N=859	N=875

Clinical Endpoints	LEQEMBI 10 mg/kg Every Two Weeks	Placebo
Mean baseline	3.17	3.22
Adjusted mean change from baseline at 18 months (%) Difference from placebo	1.21 -0.45 (-27%) (p<0.0001)	1.66
ADAS-Cog14	N=854	N=872
Mean baseline	24.45	24.37
Adjusted mean change from baseline at 18 months (%) Difference from placebo	4.140 -1.442 (-26%) (p=0.00065)	5.581
ADCS MCI-ADL	N=783	N=796
Mean baseline	41.2	40.9
Adjusted mean change from baseline at 18 months Difference from placebo	-3.5 (-37%) 2.0 (p<0.0001)	-5.5

Figure 2: Adjusted Mean Change from Baseline in CDR-SB in Study 2



16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

LEQEMBI (lecanemab-irmb) injection is a preservative-free, sterile, clear to opalescent, and colorless to pale yellow solution. LEQEMBI is supplied one vial per carton as follows:

500 mg/5 mL (100 mg/mL) single-dose vial (with white flip cap) – NDC 62856-215-01
200 mg/2 mL (100 mg/mL) single-dose vial (with dark grey flip cap) – NDC 62856-212-01

16.2 Storage and Handling

Unopened Vial

- Store in a refrigerator at 2°C to 8°C (36°F to 46°F).
- Store in the original carton to protect from light.
- Do not freeze or shake.

Diluted Solution

For storage of the diluted infusion solution, *see Dosage and Administration (2.5)*.

17 PATIENT COUNSELING INFORMATION

Advise the patient and/or caregiver to read the FDA-approved patient labeling (Medication Guide).

Amyloid Related Imaging Abnormalities

Inform patients that LEQEMBI may cause Amyloid Related Imaging Abnormalities or "ARIA". ARIA most commonly presents as a temporary swelling in areas of the brain that usually resolves over time. Some people may also have small spots of bleeding in or on the surface of the brain. Inform patients that most people with swelling in areas of the brain do not experience symptoms, however, some people may experience symptoms such as headache, confusion, dizziness, vision changes, nausea, aphasia, weakness, or seizure. Instruct patients to notify their healthcare provider if these symptoms occur. Inform patients that events of intracerebral hemorrhage greater than 1 cm in diameter have been reported infrequently in patients taking LEQEMBI, and that the use of anticoagulant or thrombolytic medications while taking LEQEMBI may increase the risk of bleeding in the brain. Notify patients that their healthcare provider will perform MRI scans to monitor for ARIA *[see Warnings and Precautions (5.1)]*.

Inform patients that although ARIA can occur in any patient treated with LEQEMBI, there is an increased risk in patients who are ApoE ε4 homozygotes and that testing for ApoE ε4 status should be performed prior to initiation of treatment to inform the risk of developing ARIA. Prior to testing, discuss with patients the risk of ARIA across genotypes and the implications of genetic testing results. Inform patients that if testing is not performed, it cannot be determined if they are ApoE ε4 homozygotes and at a higher risk for ARIA.

Patient Registry

Advise patients that the Alzheimer's Network for Treatment and Diagnostics (ALZ-NET) is a voluntary provider-enrolled patient registry that collects information on treatments for Alzheimer's disease, including LEQEMBI. Encourage patients to participate in the ALZ-NET registry *[see Warnings and Precautions (5.1)]*.

Hypersensitivity Reactions

Inform patients that hypersensitivity reactions, including angioedema and anaphylaxis have occurred in patients who were treated with LEQEMBI. Advise patients to see immediate medical attention if they experience any symptoms of serious or severe hypersensitivity reactions *[see Warnings and Precautions (5.2)]*.

Infusion-Related Reactions

Advise patients of the potential risk of infusion-related reactions, which can include flu-like symptoms, nausea, vomiting, and changes in blood pressure, the majority of which occur with the first infusion *[see Warnings and Precautions (5.3)]*.

Manufactured by:
Eisai Inc.
Nutley, NJ 07110
U.S. License No. 1862

LEQEMBI® is a registered trademark of Eisai R&D Management Co., Ltd.

MEDICATION GUIDE
LEQEMBI® (leh-kem'-bee)
(lecanemab-irmb)
injection, for intravenous use

What is the most important information I should know about LEQEMBI?
LEQEMBI can cause serious side effects including:

- **Amyloid Related Imaging Abnormalities or "ARIA". ARIA is a side effect that does not usually cause any symptoms but serious symptoms can occur.** ARIA is most commonly seen as temporary swelling in areas of the brain that usually resolves over time. Some people may also have small spots of bleeding in or on the surface of the brain, and infrequently, larger areas of bleeding in the brain can occur. Most people with this type of swelling in the brain do not get symptoms, however some people may have symptoms, such as:
  - headache
  - confusion
  - dizziness
  - vision changes
  - nausea
  - difficulty walking
  - seizures

Some people have a genetic risk factor (homozygous apolipoprotein E gene carriers) that may cause an increased risk for ARIA. Talk to your healthcare provider about testing to see if you have this risk factor.

Some medicines can increase the risk for larger areas of bleeding in the brain in patients taking LEQEMBI. Talk to your healthcare provider to see if you are on any medicines that increase this risk.

Your healthcare provider will do magnetic resonance imaging (MRI) scans before and during your treatment with LEQEMBI to check you for ARIA.

Call your healthcare provider or go to the nearest hospital emergency room right away if you have any of the symptoms listed above.

What is LEQEMBI?
LEQEMBI is a prescription medicine used to treat people with Alzheimer's disease.
It is not known if LEQEMBI is safe and effective in children.

Do not receive LEQEMBI if you:

- have serious allergic reactions to lecanemab-irmb or to any of the ingredients in LEQEMBI. See the end of this Medication Guide for a complete list of ingredients in LEQEMBI.

Before receiving LEQEMBI, tell your healthcare provider about all of your medical conditions, including if you:

- are pregnant or plan to become pregnant. It is not known if LEQEMBI will harm your unborn baby. Tell your healthcare provider if you become pregnant during your treatment with LEQEMBI.
- are breastfeeding or plan to breastfeed. It is not known if lecanemab-irmb (the active ingredient in LEQEMBI) passes into your breast milk. Talk to your healthcare provider about the best way to feed your baby while receiving LEQEMBI.

Tell your healthcare provider about all of the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.
Especially tell your healthcare provider if you take medicines to reduce blood clots from forming (antithrombotic medicines, including aspirin). Ask your healthcare provider for a list of these medicines if you are not sure.
Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist when you get a new medicine.

How will I receive LEQEMBI?

- LEQEMBI is given by a healthcare provider through a needle placed in your vein (intravenous (IV) infusion) in your arm.
- LEQEMBI is given every 2 weeks. Each infusion will last about 1 hour.
- If you miss an infusion of LEQEMBI, you should receive your next dose as soon as possible.

What are the possible side effects of LEQEMBI?
LEQEMBI can cause serious side effects, including:

- **see "What is the most important information I should know about LEQEMBI?"**

- **Serious allergic reactions.** Swelling of the face, lips, mouth, or tongue, hives, or difficulty breathing have happened during a LEQEMBI infusion. Tell your healthcare provider if you have any symptoms of a serious allergic reaction during or after LEQEMBI infusion.
- **infusion-related reactions. Infusion-related reactions are a common side effect which can be serious. Tell your healthcare provider right away if you get these symptoms during an infusion of LEQEMBI:**
  - fever
  - flu-like symptoms (chills, body aches, feeling shaky and joint pain)
  - nausea
  - vomiting
  - dizziness or lightheadedness
  - changes in your heart rate or feel like your chest is pounding
  - difficulty breathing or shortness of breath

If you have an infusion-related reaction, your healthcare provider may give you medicines before your LEQEMBI infusions to decrease your chance of having an infusion-related reaction. These medicines may include antihistamines, anti-inflammatory medicines, or steroids.

The most common side effects of LEQEMBI include:

- infusion-related reactions
- swelling in areas of the brain, with or without small spots of bleeding in or on the surface of the brain (ARIA)
- headache

These are not all the possible side effects of LEQEMBI. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

General information about the safe and effective use of LEQEMBI.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. You can ask your pharmacist or healthcare provider for information about LEQEMBI that is written for healthcare professionals.

There is a registry that collects information on treatments for Alzheimer's disease. The registry is named ALZ-NET (Alzheimer's Network for Treatment and Diagnostics). Your healthcare provider can help you become enrolled in this registry.

What are the ingredients in LEQEMBI?

Active ingredient: lecanemab-irmb.

Inactive ingredients: arginine hydrochloride, histidine, histidine hydrochloride monohydrate, polysorbate 80, and water for injection.

Manufactured by:
Eisai Inc.
Nutley, NJ 07110
U.S. License No. 1862

For more information, go to www.LEQEMBI.com or call 1-888-274-2378.

This Medication Guide has been approved by the U.S. Food and Drug Administration. Revised: 7/2023

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/s/

TERESA J BURACCHIO
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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761269Orig1s001

OFFICER/EMPLOYEE LIST

Officer/Employee List
sBLA 761269 s001

The following officers or employees of FDA participated in the decision to approve this application and consented to be identified on this list:

Alfaro, Cara
Bhattaram, Atul
Erten-Lyons, Deniz
Freed, Lois
Freilich, Emily
Jackson, Kelly
Jawidzik, Laura
Krudys, Kevin
Mani, Ranjit
Papanastasiou, Emilios Andrew
Rogers, Hobart
Sabarinath, Sreedharan
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Toscano, Christopher
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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761269Orig1s001

SUMMARY REVIEW

Summary Memorandum

Date	July 6, 2023
From	Ranjit Mani, MD Cross-Discipline Team Lead, Division of Neurology 1 (DN1) Sally Jo Yasuda, PharmD Deputy Director for Safety, DN1 Emily Freilich, MD Director, DN1 Teresa Buracchio, MD Director (acting) Deputy Director Office of Neuroscience
Subject	Summary Memorandum
BLA #	761269/s001
Applicant	Eisai Inc
Date of Submission	January 6, 2023
PDUFA Goal Date	July 6, 2023
Proprietary Name	Leqembi
Established or Proper Name	lecanemab
Dosage Form(s)	Solution for injection
Applicant Proposed Indication(s)/Population(s)	treatment of Early Alzheimer's Disease (mild cognitive impairment due to AD and mild AD dementia, with confirmed amyloid pathology)
Applicant Proposed Dosing Regimen(s)	10 mg/kg as an intravenous infusion every two weeks
Recommendation on Regulatory Action	Traditional Approval
Recommended Indication(s)/Population(s) (if applicable)	Treatment of Alzheimer's disease

1. Benefit-Risk Assessment

Benefit-Risk Assessment Framework

Benefit-Risk Integrated Assessment

Alzheimer's disease (AD) is a neurodegenerative disease that causes progressive impairments in memory, language, and thinking, with the eventual loss of ability to perform social and functional activities in daily life. In general, the average survival is 4 to 8 years after a diagnosis of dementia due to AD. It is estimated that 6.7 million Americans age 65 and older are currently living with AD dementia, and AD is a leading cause of death in the United States. Currently approved treatments for AD include the cholinesterase inhibitors donepezil, rivastigmine, and galantamine, and the N-methyl-D-aspartate (NMDA) receptor antagonist, memantine. These drugs provide modest benefits to patients with AD, but it is unclear if these drugs slow or prevent neurodegeneration in patients with AD. Aducanumab and lecanemab are anti-amyloid beta-directed antibodies approved under the accelerated approval pathway for the treatment of treatment of Alzheimer's disease, with use specifically recommended for patients with mild cognitive impairment or mild dementia stage of disease. These approvals were based on a demonstration of reduction of amyloid beta on PET imaging, a surrogate endpoint that was determined to be reasonably likely to predict clinical benefit. There is an urgent and unmet medical need for effective treatments for AD, and a particular unmet need for therapies in AD that slow, halt, reverse, prevent, or cure the disease, with an important focus on the development on drugs that target the underlying pathophysiology of AD in an effort to fundamentally affect the course of the disease.

Lecanemab (previously BAN2401) is a humanized immunoglobulin G1 (IgG1) anti-amyloid beta (Aβ) monoclonal antibody targeting aggregated forms of Aβ. Extracellular deposits of Aβ, referred to as amyloid plaques, are one of the pathologic hallmarks of AD, along with intracellular aggregates of hyperphosphorylated tau in the form of neurofibrillary tangles. Accumulation of Aβ in the brain has been proposed to be the primary driver of the disease process and precedes the accumulation of tau pathology and neural degeneration.

The Applicant is seeking conversion of the current accelerated approval to a traditional approval based on results from Study 301 (CLARITY-AD), a Phase 3 multicenter, randomized, double-blind, placebo-controlled, parallel-group study in subjects with mild cognitive impairment or mild dementia due to Alzheimer's disease. Subjects were required to have evidence of brain Aβ pathology by either visual read of a positron emission tomography (PET) scan or CSF assessment of t-tau/Aβ1-42. The study included a 60-day screening period, an 18-month (78-week) placebo-controlled period, and a safety follow-up period of 3

months after the final dose. Subjects were randomized to placebo or 10 mg/kg biweekly lecanemab in a 1:1 ratio in the placebo-controlled period. The primary clinical endpoint was the change from baseline in Clinical Dementia Rating Scale- sum of boxes (CDR-SB) at Week 79. Secondary endpoints included the change from baseline in brain amyloid plaque levels as measured by PET, and change from baseline in Alzheimer's Disease Assessment Scale – Cognitive Subscale (ADAS-Cog 14), Alzheimer's Disease Composite Score (ADCOMS), and Alzheimer's Disease Cooperative Study – Activities of Daily Living – Mild Cognitive Impairment (ADCS-ADL-MCI) at 18 months.

The primary efficacy endpoint analysis, change from baseline in CDR-SB at Week 79, demonstrated a statistically significant treatment effect in the lecanemab treatment arm compared to placebo in the FAS+ population (-0.45[-27%], p=0.00005 and the FDA FAS population (-0.39[-25%], p=0.0004). Nominal statistical significance was reached by Week 27 and maintained through Week 79. Results were robust across sensitivity analyses. Statistically significant results favoring lecanemab were observed for all 3 multiplicity-controlled secondary clinical endpoints. Lecanemab resulted in a reduction in change from baseline as measured on the ADAS-Cog 14 (-1.442[-26%], p=0.00065), ADCS-ADL-MCI (2.016[-37%], p<0.00001), and ADCOMS (-0.050[-24%], p=0.00002) as compared to placebo. Amyloid PET was assessed in 40% of the overall population (353 subjects in the placebo arm and 363 subjects in the lecanemab treatment arm). Lecanemab treatment demonstrated a statistically significant treatment effect on change from baseline in brain amyloid as measured by PET and reported as Centiloids at Week 79 (-59.1, p<0.00001).

An exploratory subgroup analysis in ApoE ε4 homozygotes showed no clinical benefit on the CDR-SB; however, there were trends for efficacy on the ADAS-cog and ADCS-ADL-MCI scale that were lower than heterozygotes and non-carriers. There were favorable trends for treatment effects in health-related outcome measures and biomarkers in the homozygote subgroup. Overall, the data appear to suggest a treatment benefit in ApoE ε4 homozygotes although there are uncertainties about the magnitude of benefit in this subgroup relative to heterozygotes and noncarriers.

Lecanemab received accelerated approval based on data from Study 201 that demonstrated substantial evidence of effectiveness on a reasonably likely surrogate endpoint, reduction in brain amyloid beta plaques as measured by PET imaging. The results of Study 301 verify and describe the clinical benefit of lecanemab for the treatment of Alzheimer's disease. The collective evidence from Study 201 and 301 continue to demonstrate substantial evidence of effectiveness for lecanemab for the treatment of Alzheimer's disease, and support the traditional approval of lecanemab in this population. The effect on the primary endpoint represents a clinically meaningful reduction of clinical decline. The finding on the primary endpoint is supported by statistically significant results for all 4 multiplicity-controlled secondary endpoints, including endpoints capturing distinct information regarding cognitive decline. The treatment effect in Study 301 is supported by the consistently favorable results for the primary and secondary endpoints across subgroups of interest defined by demographic and baseline disease

characteristics. Biomarkers reflecting target engagement, effects on downstream tau pathophysiology, and neurodegeneration support the observations on the clinical endpoints.

The safety of lecanemab was characterized in a safety database of adequate size.

There was no imbalance of deaths occurring within 30 days after a dose in the lecanemab-treated subjects (0.7%, 6/898) compared to placebo (0.8%, 7/897) in Study 301 Core. In 301 OLE the incidence of deaths was 0.7% (9/1385). There were 3 deaths for which a role for lecanemab cannot be ruled out:

- A high burden of cerebral amyloid angiopathy (CAA) and findings consistent with an inflammatory vasculitis were identified on autopsy in 2 subjects who were ApoE ε4 homozygotes on lecanemab, both of whom complained of headaches shortly after exposure to lecanemab, and one of whom had cerebral hemorrhage.
- An additional death with possible CAA occurred in an ApoE ε3 homozygote with cerebral hemorrhage in the setting of confounding factors including anticoagulant use.
- The inflammatory vasculitis in the 2 cases with a high burden of CAA resembled CAA related inflammation (CAA-ri), a spontaneous inflammatory response to the vascular amyloid deposits which presents with symptoms and imaging findings similar to amyloid related imaging abnormalities (ARIA)

Monoclonal antibodies directed against aggregated forms of beta amyloid, such as lecanemab, can cause amyloid related imaging abnormalities (ARIA), characterized as ARIA with edema (ARIA-E), which can be observed on MRI as brain edema or sulcal effusions, and ARIA with hemosiderin deposition (ARIA-H), which includes microhemorrhage and superficial siderosis. ARIA can occur spontaneously in patient with AD or with CAA. The risk of both severe CAA and CAA-ri is highest in ApoE ε4 homozygotes. The risk of lecanemab use in patients with CAA is not well characterized.

ARIA was observed in 21% of subjects treated with lecanemab 10 mg/kg biweekly (191 out of 898) compared to 9% subjects on placebo (84 out of 897) in Study 301 Core. Symptomatic ARIA occurred in 3% (29/898) of subjects treated with lecanemab compared to 0.2% (2/897) on placebo in Study 301 Core. The most common symptom was headache; other reported symptoms included confusion, dizziness, nausea, visual changes, and focal neurologic deficits, consistent with symptoms reported for this class of drugs.

ARIA-E was observed in 13% (113/898) of subjects treated with lecanemab 10 mg/kg biweekly compared to 2% (15/897) of subjects on placebo in Study 301 Core. Among the 898 subjects treated with lecanemab 10 mg/kg biweekly, the maximum radiographic severity was mild in 4% (37/898), moderate in 7% (66/898), and severe in 1% (9/898). The majority of ARIA-E

radiographic events occurred early in treatment (within the first 7 doses). After detection, resolution occurred in 52 % of ARIA-E subjects by 12 weeks, 81% by 17 weeks, and 100% overall.

ARIA-H was observed in 17% (152/898) of subjects on lecanemab 10 mg/kg biweekly compared to 9% (80/897) of subjects on placebo in Study 301 Core. There was no imbalance in isolated ARIA-H for lecanemab compared to placebo.

In Study 301 Core, 16% (141/898) of subjects in the lecanemab arm were apolipoprotein E ε4 (ApoE ε4) homozygotes, 53% (479/898) were heterozygotes, and 31% (278/898) were noncarriers, representative of the general population with AD. The incidence of ARIA in Study 301 Core was higher in ApoE ε4 homozygotes (45% on lecanemab vs. 22% on placebo) than in heterozygotes (19% on lecanemab vs 9% on placebo) and noncarriers (14% on lecanemab vs 4% on placebo). Among subjects treated with lecanemab, symptomatic ARIA-E occurred in 9% of ApoE ε4 homozygotes compared with 2% of heterozygotes and 1% noncarriers. Serious events of ARIA occurred in 3% of ApoE ε4 homozygotes, and approximately 1% of heterozygotes and noncarriers. Among subjects treated with lecanemab who had ARIA E, severe radiographic ARIA-E was greatest in APO E ε4 homozygotes (15%, 7/46) compared to heterozygotes (4%, 2/51) or noncarriers (0/30). Among subjects treated with lecanemab who had ARIA H, severe radiographic ARIA H was greatest in Apo E ε4 homozygotes (35%, 19/54) compared to heterozygotes (14%, 9/66) or noncarriers (9%, 3/32).

Intracerebral hemorrhage greater than 1 cm in diameter was reported in 0.7% (6/898) subjects on lecanemab and in 0.1% (1/897) subjects on placebo in Study 301 Core. Fatal events of intracerebral hemorrhage in subjects taking lecanemab were reported in the 301 OLE as noted above.

There was no increased risk of ARIA-H in subjects who received lecanemab 10 mg/kg biweekly and an antithrombotic medication compared to subjects who received placebo and an antithrombotic medication. The incidence of intracerebral hemorrhage was 0.9% (3/328 subjects) in subjects taking lecanemab with a concomitant antithrombotic medication at the time of the event compared to 0.6% (3/545 subjects) in those who did not receive an antithrombotic. Subjects taking lecanemab with an anticoagulant alone or combined with an antiplatelet medication or aspirin had an incidence of intracerebral hemorrhage of 2.5% (2/79 subjects) compared to none in subjects who received placebo.

Hypersensitivity reactions, including angioedema, bronchospasm, and anaphylaxis occurred in subjects treated with lecanemab in 301 Core. Infusion-related reactions occurred in 26% (237/898) of subjects on lecanemab vs. 7% (66/897) in placebo-treated subjects in Study 301 Core. Infusion reactions were mostly mild (69%) or moderate (28%) in severity, and 75% occurred at the time of the first infusion. Symptoms were consistent with those identified in currently approved labeling for lecanemab. Most subjects with an infusion reaction (94%, 221/236) received subsequent infusions. Forty four percent (97/221) received at least

1 preventative medication with subsequent infusions. The incidence of subsequent infusion-related reactions after a first event on lecanemab was similar with (37%, 36/97) and without (35%, 43/124) preventative medication.

The most common adverse drug reactions with lecanemab are infusion-related reactions, ARIA-H, ARIA-E, and headache. All occurred in at least 10% of subjects on lecanemab and at least 2% more frequently than placebo in the controlled period of Study 301. This was consistent with the most common adverse reactions observed in Study 201 Core.

In summary, the results of Study 301 verify and describe the clinical benefit of lecanemab for the treatment of Alzheimer's disease. The collective evidence from Study 201 and 301 continue to demonstrate substantial evidence of effectiveness for lecanemab for the treatment of Alzheimer's disease, and support the traditional approval of lecanemab in this population. The data from Study 301 are adequate to fulfill the postmarketing requirement 4384-1 to verify the clinical benefit of lecanemab.

ARIA and infusion reactions are the primary risks associated with the use of lecanemab. ARIA is usually asymptomatic. When symptomatic ARIA occurs, symptoms are usually mild or moderate, though serious asymptomatic (i.e., radiographic) and symptomatic cases can occur. The incidence of ARIA, including symptomatic ARIA, was higher in ApoE ε4 homozygotes compared to heterozygotes and noncarriers. Risk management for ARIA can be achieved through clear product labeling and monitoring for ARIA, as described in the label. A Boxed Warning will describe the overall risk of ARIA with lecanemab treatment and will highlight the increased risk of ARIA, including symptomatic, serious, and severe radiographic ARIA, in ApoE ε4 homozygotes. The Boxed Warning will also describe fatal intracerebral hemorrhages that have occurred in subjects treated with lecanemab. ARIA will also be further described in Section 5.1 Warnings and Precautions. The label will state that testing for ApoE ε4 status should be performed prior to initiation of treatment with lecanemab to inform the risk of developing ARIA. Postmarketing requirements (PMRs) will be imposed to further characterize risk factors for adverse outcomes associated with ARIA. A postmarketing commitment (PMC) will be agreed upon for development of a test for Apo E ε4 genotype. Enhanced pharmacovigilance will be performed to more fully characterize ARIA in the practice setting. Infusion-related reactions occurring in the controlled trial were moderate or mild, primarily occurring with first dose, and subsequently prevented in some cases by pre-treatment. Infusion reactions will receive a warning in labeling. There are no safety issues that preclude approval.

Lecanemab is indicated for the treatment of Alzheimer's disease; however, the indication statement notes that treatment should be initiated in patients with mild cognitive impairment or mild dementia stage of disease, the population in which treatment was initiated in clinical trials. It is appropriate to indicate the drug for the treatment of Alzheimer's disease because the disease exists on a spectrum and there may not be clear distinctions between one stage and another. For example, a patient does not change from mild to moderate dementia at a discrete timepoint, but there is a slow progression of the disease with overlying waxing and waning of cognitive and behavioral symptoms. Therefore, it will require clinical judgement for the

prescriber regarding whether a patient is at an appropriate stage of disease for treatment and if there is a suggestion of clinical benefit that may warrant continued treatment despite progression of the disease.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Alzheimer's disease is a progressive, degenerative brain disorder that affects memory, thinking, and behavior and is the most common cause of dementia. • Clinical symptoms include difficulty remembering recent conversations, names or events, impaired communication, disorientation, confusion, poor judgment, behavioral changes, and ultimately, difficulty walking, speaking, and swallowing. • Alzheimer's disease exists on a continuum from biological changes in the brain, to subtle problems with memory and thinking, and ultimately difficulties that affect an individual's ability to perform everyday activities. The disease process may begin 20 years or more before symptoms arise. • After a diagnosis of Alzheimer's dementia, the average survival is 4 to 8 years. • An estimated 6.7 million Americans age 65 and older are currently living with Alzheimer's disease. • Alzheimer's disease is a leading cause of death in the United States. • Almost two-thirds of Americans with Alzheimer's disease are women. Older African Americans and Latinos are disproportionately more likely to have Alzheimer's disease than White Americans.	Alzheimer's disease is a major public health issue which imposes an immense burden on patients and caregivers. The number of Americans with Alzheimer's disease dementia is expected to increase significantly in the next few decades.
Current Treatment Options	• FDA-approved therapies include the acetylcholinesterase inhibitors donepezil, rivastigmine, and galantamine, and the N-methyl-D-aspartate receptor antagonist memantine. Treatment effects of these therapies are modest and transitory. • Aducanumab and lecanemab are anti-amyloid beta-directed antibodies approved under the accelerated approval pathway for the treatment of Alzheimer's disease, with use specifically recommended for patients with mild cognitive impairment or mild dementia stage of disease. These approvals were based on a demonstration of reduction of amyloid beta plaque on PET imaging, a surrogate endpoint that was determined to be reasonably likely to predict clinical benefit.	There is an urgent and unmet medical need for effective treatments for Alzheimer's disease. In addition to the general need for more effective treatments, there is a particular unmet need for effective treatments to delay, halt, or reverse the pathophysiological processes that ultimately lead to the clinical deficits of Alzheimer's disease.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• Antipsychotics are commonly prescribed to treat behavioral symptoms but are not approved for the treatment of Alzheimer's disease and are associated with increased mortality in older patients.	

Benefit	• The efficacy of lecanemab in patients at the early stages of symptomatic Alzheimer's disease was evaluated in Study 301.
	  • Participants were randomized 1:1 to receive placebo or 10 mg/kg lecanemab as an IV infusion once every two weeks.
	  • The trial enrolled 1795 subjects: 898 in the lecanemab treatment arm and 897 in the placebo arm.
	  • The primary endpoint was the change from baseline in CDR-SB at Week 79. CDR-SB is an integrated scale that meaningfully assesses both daily function and cognitive effects. Key secondary endpoints were change from baseline to Week 79 in amyloid PET using Centiloids, ADAS-Cog 14, ADCOMS, and ADCS-ADL-MCI.
	  • Exploratory endpoints included health-related quality of life measures.
	  • Key pharmacodynamic endpoints included change from baseline in tau PET, brain volumes as measured by volumetric MRI, and fluid biomarkers of amyloid, tau, and neurodegeneration.
	• Treatment with lecanemab demonstrated reduced clinical decline, as evidenced by a statistically significant treatment effect on change from baseline in CDR-SB compared to placebo (-0.45 [-27%], p=0.00005).
	• The lecanemab treatment arm had a statistically significant reduction in brain amyloid from baseline to Week 79 compared to the placebo arm (mean difference -59.9 Centiloid; p<0.00001).
	• Statistically significant treatment effects in favor of lecanemab were observed for all multiplicity-controlled secondary clinical endpoints at Week 79: ADAS-Cog 14 (-1.442 [-26%], p=0.00065), ADCOMS (-0.05, [-24%], p=0.00002), and ADCS-ADL-MCI (2.016 [-37%], p<0.0001).
	• Results were robust to sensitivity analyses.
	• Treatment effects on biomarkers reflecting brain amyloid, downstream Alzheimer's tau pathophysiology, and neurodegeneration supported the
		The results of Study 301 confirm the clinical benefit of lecanemab for the treatment of Alzheimer's disease. The effect on the primary endpoint represents a clinically meaningful reduction of clinical decline. The finding on the primary endpoint is supported by statistically significant results for all 4 multiplicity-controlled secondary endpoints, including endpoints capturing distinct information regarding cognitive decline. The treatment effect in Study 301 is supported by the consistently favorable results for the primary and secondary endpoints across subgroups of interest defined by demographic and baseline disease characteristics. Biomarkers reflecting target engagement, effects on downstream tau pathophysiology, and neurodegeneration support the observations on the clinical endpoints.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	observations on clinical outcomes • Favorable results were observed for the primary endpoint across subgroups of interest, with the exception of homozygous ApoE ε4 carriers. Results in homozygous ApoE ε4 carriers for secondary clinical endpoints, biomarkers, and health outcome assessments, however, support a favorable treatment effect in this subgroup.	
Risk and Risk Management	• The safety database includes 2345 subjects exposed to at least one dose of lecanemab at any dose and 2090 subjects exposed to at least 1 dose lecanemab 10 mg/kg. This includes 1604 subjects with Mild Cognitive Impairment (MCI) due to AD and mild dementia due to AD treated with lecanemab 10 mg/kg biweekly for at least 6 months, 1261 subjects for at least 12 months, and 965 subjects for at least 18 months. • There was no imbalance of deaths occurring within 30 days after a dose in the lecanemab-treated subjects (0.7%, 6/898) compared to placebo (0.8%, 7/897) in Study 301 Core. There were no deaths preceded by ARIA in 301 Core. In 301 OLE the incidence of deaths was 0.7% (9/1385). There were 3 deaths for which a role for lecanemab cannot be ruled out: ○ A high burden of cerebral amyloid angiopathy (CAA) and findings consistent with an inflammatory vasculitis were identified on autopsy in 2 subjects who were ApoE ε4 homozygotes, both of whom complained of headaches shortly after exposure to lecanemab. ○ An additional death with possible CAA occurred in an ApoE ε3 homozygote with cerebral hemorrhage in the setting of confounding factors, including anticoagulant use. ○ The inflammatory vasculitis in the 2 cases with a high burden of CAA resembled CAA related inflammation (CAA-ri), a spontaneous inflammatory response to the vascular amyloid deposits which presents with symptoms and imaging findings similar to ARIA-E and ARIA-H. • The most common TEAEs in Study 301 Core (at least 5% and at least 2% greater than placebo) were infusion-related reactions (26%), ARIA-H (14%), ARIA-E (13%), headache (11%), superficial siderosis of the central nervous system (6%), and rash (6%). This was generally consistent with the TEAEs	The safety database fulfills minimum ICH guidance. Risk management for ARIA can be achieved through clear product labeling and monitoring for ARIA, as described in the label. A Boxed Warning will describe the overall risk or ARIA with lecanemab treatment and highlight the increased risk of ARIA, including symptomatic, serious, and severe radiographic ARIA, in ApoE ε4 homozygotes. The Boxed Warning will also describe fatal intracerebral hemorrhages that have occurred in subjects treated with lecanemab. The label will state that testing for ApoE ε4 status should be performed prior to initiation of treatment with lecanemab to inform the risk of developing ARIA. A Warnings and Precautions Section 5.1 of the prescribing information will alert prescribers to the risk of ARIA and its symptoms when they occur and that the risk of ARIA, including symptomatic ARIA, was higher in ApoE ε4 homozygotes, providing details that support the Boxed Warning. Guidance regarding monitoring and implications regarding a finding of ARIA on subsequent dosing will be

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	observed in Study 201 Core. • ARIA was observed in 21 % (19/898) of subjects treated with lecanemab 10 mg/kg biweekly, compared to 9 % (84/897) of subjects on placebo in Study 301 Core. • The incidence of ARIA in Study 301 Core was higher in ApoE ε4 homozygotes (45% on lecanemab vs. 22% on placebo) than in heterozygotes (19% on lecanemab vs 9% on placebo) and noncarriers (14% on lecanemab vs 4% on placebo). ○ Among subjects treated with lecanemab, symptomatic ARIA-E occurred in 9% of ApoE ε4 homozygotes, compared with 2% of heterozygotes and 1% of noncarriers. ○ Serious events of ARIA occurred in 3% of ApoE ε4 homozygotes, and approximately 1% of heterozygotes and noncarriers. ○ Among subjects treated with LEQEMBI who had ARIA E, severe radiographic ARIA-E was greatest in Apo E ε4 homozygotes (15%, 7/46) compared to heterozygotes (4%, 2/51) or noncarriers (0/30). ○ Among subjects treated with lecanemab who had ARIA-H, severe radiographic ARIA-H was greatest in Apo E ε4 homozygotes (35%, 19/54) compared to heterozygotes (14%, 9/66) or noncarriers (9%, 3/32). • Symptomatic ARIA occurred in 3% (29/898) of subjects treated with lecanemab compared to 0.2% (2/897) on placebo in Study 301 Core. The most common symptom was headache; other reported symptoms included confusion, dizziness, nausea, visual changes, and focal neurologic deficits, consistent with symptoms reported for this class of drugs. • ARIA-E was observed in 13% (113/898) of subjects treated with lecanemab 10 mg/kg biweekly compared to 2% (15/897) of subjects on placebo in Study 301 Core. Among the 898 subjects treated with lecanemab 10 mg/kg biweekly, the maximum radiographic severity was mild in 4% (37/898), moderate in 7% (66/898), and severe in 1%	provided in Section 2.3 of the prescribing information. MRI prior to the 5th, 7th, and 14th infusions will be utilized to identify asymptomatic ARIA. The Warning will describe the increased incidence of intracerebral hemorrhage in subjects taking lecanemab with a concomitant antithrombotic medication, in particular an anticoagulant. • Enhanced clinical vigilance is recommended with additional guidance for considerations regarding continued treatment. Because intracerebral hemorrhage > 1 cm in diameter has been observed in subjects taking lecanemab, prescribers will be advised to exercise additional caution when considering the administration of anticoagulants or thrombolytic agents (e.g., tissue plasminogen activator) to a patient already being treated with lecanemab. • The label will recommend caution when considering use of lecanemab in patients that indicate an increased risk for intracerebral hemorrhage including the presence of an Apo E ε4 allele, findings on neuroimaging suggestive of CAA, or other lesions that could potentially increase the risk of intracerebral hemorrhage. The risk of ARIA, including the recommendation for Apo E ε4 testing and the risk for concomitant use of anticoagulants will also be addressed in the Medication Guide.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	(9/898). The majority of ARIA-E radiographic events occurred early in treatment (within the first 7 doses). After detection, resolution occurred in 52 % of ARIA-E subjects by 12 weeks, 81% by 17 weeks, and 100% overall. • ARIA-H was observed in 17% (152/898) of subjects on lecanemab 10 mg/kg biweekly compared to 9% (80/897) of subjects on placebo in Study 301 Core. There was no imbalance in isolated ARIA-H for lecanemab compared to placebo. • Intracerebral hemorrhage greater than 1 cm in diameter was reported in 0.7% (6/898) subjects on lecanemab and in 0.1% (1/897) subjects on placebo in Study 301 Core. Fatal events of intracerebral hemorrhage in subjects taking lecanemab were reported in the 301 OLE as noted above. • There was no increased risk of ARIA-H in subjects who received lecanemab 10 mg/kg biweekly and an antithrombotic medication compared to subjects who received placebo and an antithrombotic medication. • The incidence of intracerebral hemorrhage was 0.9% (3/328 subjects) in subjects taking lecanemab with a concomitant antithrombotic medication at the time of the event compared to 0.6% (3/545 subjects) in those who did not receive an antithrombotic. Subjects taking lecanemab with an anticoagulant alone or combined with an antiplatelet medication or aspirin had an incidence of intracerebral hemorrhage of 2.5% (2/79 subjects) compared to none in subjects who received placebo. • Hypersensitivity reactions, including angioedema, bronchospasm, and anaphylaxis occurred in subjects treated with lecanemab in 301 Core. • Infusion-related reactions occurred in 26% (237/898) of subjects on lecanemab vs. 7% (66/897) in placebo-treated subjects in Study 301 Core. Infusion reactions were mostly mild (69%) or moderate (28%) in severity, and 75% occurred at the time of the first infusion. Symptoms were consistent with those identified in currently approved labeling for lecanemab. Most subjects with an infusion reaction (94%, 221/236) received subsequent infusions. Forty four percent (97/221) received at least 1 preventative medication with subsequent infusions. The incidence of subsequent	Prescribers will be made aware of the risk of hypersensitivity in Section 5.2 and of infusion-related reactions in Section 5.3 of Warnings and Precautions. A history of a serious hypersensitivity reaction to lecanemab will be a contraindication. This will also be addressed in the Medication Guide. Postmarketing requirements (PMRs) will be imposed to further characterize risk factors for adverse outcomes associated with ARIA. A postmarketing commitment (PMC) will be agreed upon for development of a test for Apo E ε4 genotype. Requested postmarketing vigilance will further characterize the uncertainties related to safety of lecanemab.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	infusion-related reactions after a first event on lecanemab was similar with (37%, 36/97) and without (35%, 43/124) preventative medication. Uncertainties • Patients with moderate or severe dementia were excluded from the key studies analyzed for review of safety; therefore, safety outcomes in these patients are unknown. • Whether the risk of ARIA or intracerebral hemorrhage in patients with AD treated with lecanemab is higher in those with co-existing cerebral amyloid angiopathy (CAA) pathology is not known. Although the population that was treated would have included patients with CAA given that up to 90% of patients with AD are reported to have some degree of underlying CAA, it is currently not possible to prospectively identify those patients to understand how CAA impacts risk. • The safety of treating AD in patients with Down's syndrome is not known. • The optimal timing and frequency of MRI monitoring as a tool for mitigating ARIA is unknown. • The safety of treating patients with lecanemab through episodes of radiographically mild ARIA-E with mild clinical symptoms is unknown. • The safety of treating patients with lecanemab through episodes of radiographically mild, asymptomatic ARIA-H is unknown. • The safety of concomitant use of medications that increase bleeding risk is not well characterized. The risk of using lecanemab in patients otherwise at risk for bleeding (e.g., the presence of an ApoE ε4 allele, the presence of CAA or other lesions such as aneurysm or vascular malformation) is not known.	

2. Background

This supplemental application under review is for lecanemab, proposed for the treatment of Alzheimer's disease (AD). Lecanemab is a humanized, immunoglobulin gamma 1 (IgG1) monoclonal antibody administered by intravenous (IV) infusion that targets aggregated forms of amyloid beta. Lecanemab received accelerated approval on January 6, 2023 with the proprietary name Leqembi. This application contains the results of the confirmatory study to verify and describe the clinical benefit of lecanemab. Lecanemab is not marketed in any other country.

AD is a neurodegenerative disease that causes progressive impairments in memory, language, and thinking, with the eventual loss of ability to perform social and functional activities in daily life. Survival after a diagnosis of dementia due to AD generally ranges between 4 and 8 years; however, life expectancy can be influenced by other factors, such as comorbid medical conditions. It is estimated that 6.7 million Americans age 65 and older are currently living with Alzheimer's disease dementia, and the number is projected to reach over 12.7 million by 2050, in the absence of interventions to prevent or slow the disease (Alzheimer's Association, 2023).

The pathologic hallmarks of AD are extracellular deposits of β-amyloid (Aβ), referred to as amyloid plaques, and intracellular aggregates of hyperphosphorylated tau in the form of neurofibrillary tangles. Accumulation of Aβ in the brain is generally thought to be the primary driver of the disease process, and precedes the accumulation of tau pathology and neurodegeneration. The pathophysiological changes and clinical manifestations of AD are progressive and occur along a continuum, and accumulation of Aβ may begin 20 years or more before symptoms arise (Vermunt et al., 2019). Based on these findings, National Institute on Aging—Alzheimer's Association (NIA-AA) research criteria have been recently developed for the diagnosis and staging severity of AD, based on neuropathologic biomarker-based findings of the presence or absence of amyloid, tau, and evidence of neurodegeneration (Jack et al., 2018). The 2018 FDA Guidance, "Early Alzheimer's Disease: Developing Drugs for Treatment Guidance for Industry", also utilizes a biomarker-based framework along with the presence of clinical signs or symptoms (from asymptomatic to overt dementia) to define stages of AD to inform guidance for drug development programs.

Currently approved AD treatments include the cholinesterase inhibitors donepezil, rivastigmine, and galantamine, that are purported to address cholinergic deficits in AD by increasing acetylcholine levels in the central nervous system (CNS), and the N-methyl-D-aspartate antagonist memantine. Memantine was approved in 2003, and is postulated to work by binding preferentially to N-methyl-D-aspartate (NMDA) receptor-operated cation channels to block persistent activation by the excitatory amino acid glutamate. These drugs provide modest benefits to patients with AD, but it is unclear whether these drugs slow or prevent neurodegeneration in patients with AD. In 2021, aducanumab, an anti-amyloid beta-directed antibody, was approved under the accelerated approval pathway for the treatment

of Alzheimer's disease, with use specifically recommended for patients with mild cognitive impairment or mild dementia stage of disease. This was followed by the accelerated approval of lecanemab is January, 2023. These approvals were based on a demonstration of reduction of brain Aβ plaque on PET imaging, a surrogate endpoint that was determined to be reasonably likely to predict clinical benefit. There remains a tremendous unmet need for therapies in AD that slow, halt, reverse, prevent, or cure the disease, with an important focus on drugs that target the underlying pathophysiology of AD in an effort to fundamentally affect the course of the disease.

There have been several anti-Aβ monoclonal antibodies studied in AD that have had negative studies in Phase 3 development; however, differences in enrollment criteria, study design, and trial endpoints make it difficult to compare them to the aducanumab and lecanemab programs. There are also significant differences between anti-Aβ monoclonal antibodies related to binding at different epitopes, and selectivity for different Aβ variants (e.g., monomers, soluble oligomers, aggregated forms) (Linse et al. 2020). The degrees of amyloid reduction in these studies has been variable. Additionally, some anti-Aβ monoclonal antibodies, including lecanemab, have been associated with the occurrence of amyloid-related imaging abnormalities (ARIA) that require special attention with respect to dosing and monitoring. ARIA covers a spectrum of findings detected on brain magnetic resonance imaging (MRI), including ARIA-edema (ARIA-E) and ARIA-hemosiderin deposition (ARIA-H).

In this BLA supplement, the Applicant is seeking traditional approval of lecanemab. This submission contains efficacy, safety, and biomarker data from Study 301, a randomized, double-blind, placebo-controlled Phase 3 study in patients with MCI due to Alzheimer's disease or mild Alzheimer's disease dementia. Study 301 is intended to satisfy postmarketing requirement 4384-1 to verify the clinical benefit of lecanemab.

3. Product Quality

The Chemistry Manufacturing and Control (CMC) review was written by Gunther Boekhoudt, PhD (primary reviewer), Samuel Mindaye, PhD (application team lead), and Jenifer Swisher, PhD (review chief).

Lecanemab-irmb is a recombinant human immunoglobulin gamma 1 (IgG1) monoclonal antibody targeting aggregated soluble and insoluble forms of amyloid beta. It is expressed in a Chinese hamster ovary (CHO) cell line. Lecanemab-irmb injection is a preservative-free, sterile, clear to opalescent, and colorless to yellow solution for intravenous infusion after dilution. It is supplied in single-dose vials available in concentrations of 500 mg/5.0 mL (100 mg/mL) or 200 mg/2 mL (100 mg/mL). No new manufacturing data were provided in this efficacy supplement. (b) (4)

(b) (4)

the Applicant agreed in the action letter of the original BLA 761269 to address these problems in PMR# 4384-2.

The CMC review team recommends approval of this supplemental BLA.

4. Nonclinical Pharmacology/Toxicology

No new nonclinical data were included in this efficacy supplement.

5. Clinical Pharmacology

An integrated Office of Clinical Pharmacology (OCP) review was written by Yifei Zhang, Ph.D. (the primary reviewer), Vishnu Sharma, Ph.D., Mohsen Rajabiabhari, Ph.D., Xiulian Du, Ph.D., Hobart Rogers, Ph.D, Atul Bhattaram, Ph.D., Yow-Ming Wang, Ph.D., Bilal AbuAsal, Ph.D., Hao Zhu, Ph.D., Sreedharan Sabarinath, Ph.D, and Ramana Uppoor, Ph.D. The final OCP signatory was Mehul Mehta, Ph.D.

The clinical pharmacology review team has concluded that the effectiveness of lecanemab was supported by the effects on brain amyloid, plasma/CSF biomarkers, and exposure-response relationships from Study 301 and Study 201. Model based exposure-response analyses for both studies demonstrated that higher exposures to lecanemab were associated with (1) greater reduction in clinical decline on CDR-SB and ADAS-Cog14; (2) greater reduction in amyloid beta plaque; and (3) greater increase in plasma Aβ42/40 ratio and greater reduction in plasma p-tau181. An association between reduction in amyloid beta plaque and clinical decline on CDR-SB and ADAS-Cog14 was also observed.

Serum lecanemab C_{max} and AUC increased in an approximately dose-proportional manner within the assessed single dose range of 0.3 mg/kg to 15 mg/kg. The mean terminal $t_{½}$ of lecanemab was 5 to 7 days when administered at 1 mg/kg or higher doses. Steady-state was achieved after 6 weeks of 10 mg/kg administered every 2 weeks, and the systemic accumulation was 1.4-fold based on AUC.

Based on the pop-PK modeling updated by including data from Study 301, the mean value (95% CI) for central volume of distribution at steady-state is 3.24 (3.18-3.30) L, and the clearance of lecanemab (95% CI) is 0.370 (0.353-0.384) L/day. Lecanemab is degraded by proteolytic enzymes and is not expected to undergo renal elimination or metabolism by hepatic enzymes. Sex, body weight, and albumin were found to impact exposure to lecanemab; however, none of these covariates were found to be clinically significant and no dose adjustment is recommended based on intrinsic factors.

The review team recommends including a text description in labeling regarding the subgroup findings by ApoE ε4 genotype, including clinical endpoints and biomarkers to inform the benefit risk assessment. In addition, the team recommends including labeling information about the availability of a test to determine ApoE ε4 genotype to assist decision making.

The OCP review team recommends approval of the BLA.

6. Clinical/Statistical- Efficacy

Kevin Krudys, Ph.D., was the clinical reviewer for this application. Tristan Massie, Ph.D., was the reviewer for the Office of Biostatistics (OB) with concurrence from John Lawrence, Ph.D., Team Leader and James (Hsien-Ming) Hung, Ph.D., Division Director.

The efficacy of lecanemab for this application was based on the results of Study 301. Study 301 was a multicenter, randomized, double-blind, placebo-controlled, parallel-group study in subjects with MCI due to AD or mild AD dementia. Randomization was stratified by clinical subgroups (MCI due to AD or mild AD dementia), ApoE ε4 carrier status (carrier or non-carrier), ongoing treatment with concurrent medications for treatment of AD (yes or no), and geographical region (North America, Europe, or Asia Pacific). At least 50% of subjects enrolled in the study were to be in the MCI due to AD subgroup. The study included a 60-day screening period, an 18-month (78-week) placebo-controlled period, and a safety follow-up period of 3 months after the final dose. Subjects were randomized to placebo or 10 mg/kg biweekly lecanemab in a 1:1 ratio in the placebo-controlled period.

Subjects who completed the placebo-controlled period and met inclusion/exclusion criteria had the option to directly enter the open-label extension (OLE) phase of the study. The OLE is planned to continue for up to 4 years.

Study Population

Study 301 enrolled subjects aged 50 to 90 years who fulfilled clinical criteria for either MCI due to AD or mild AD dementia, as defined by the 2011 National Institute on Aging-Alzheimer's Association (NIA-AA) framework (Albert et al., 2011; McKhann et al. 2011), with evidence of brain Aβ pathology by either visual read of a positron emission tomography (PET) scan or CSF assessment of $A\beta_{1-42}$. Subjects were also required to have a Clinical Dementia Rating Scale global score of 0.5 or 1.0 with a Memory Box score of 0.5 or greater, Mini-Mental State Examination (MMSE) score between 22 and 30 (inclusive), and an objective impairment in episodic memory impairment as indicated by at least 1 standard deviation below age-adjusted mean in the Wechsler-Memory Scale-IV Logical Memory (subscale) II. Subjects were excluded for any neurologic condition (other than AD) contributing to cognitive impairment, history of transient ischemic attacks, stroke, or seizures within the previous year, or presence of a bleeding disorder that is not under control. Subjects were also excluded if a brain MRI performed at screening showed evidence of any of the following: more than 4 microhemorrhages (defined as 10 mm or less at the greatest diameter), a single

macrohemorrhage greater than 10 mm at greatest diameter, an area of superficial siderosis, vasogenic edema, cerebral contusion, encephalomalacia, aneurysms, vascular malformations, infective lesions, multiple lacunar infarcts or stroke involving a major vascular territory, severe small vessel, or white matter disease or space occupying lesions or brain tumors.

Primary Clinical Endpoint

The primary efficacy endpoint was the change from baseline in CDR-SB at Week 79. The CDR-SB assesses 3 domains of cognition (memory, orientation, judgment/problem solving) and three domains of function (community affairs, home/hobbies, personal care). Scores from each domain are summed to provide the CDR-SB value ranging from 0 to 18, with higher scores indicating greater disease severity. CDR-SB is accepted by FDA as a primary outcome assessment for studies in AD intended to demonstrate substantial evidence of effectiveness.

CDR-SB assessments were conducted by a clinician not involved in subject care or management who remained blinded to results of safety assessments. All sites were asked to maintain the same rater throughout the study.

Secondary Clinical Endpoints

Amyloid PET

Change from baseline in brain amyloid plaque as measured by PET (florbetapen, florbetapir, or flutemetamol) and reported in Centiloids was assessed in a subset of subjects at Week 53 and Week 79 and listed as a key secondary endpoint in the protocol.

Alzheimer's Disease Assessment Scale- cognitive subscale (ADAS-Cog)

The ADAS-Cog is a cognitive assessment consisting of clinical ratings and cognitive tasks measuring disturbances of memory, language, and praxis. The scale ranges from 0 to 90, with higher scores indicating greater disease severity.

Alzheimer's Disease Cooperative Study - Activities of Daily Living Scale for use in Mild Cognitive Impairment (ADCS-ADL-MCI)

The ADCS-ADL-MCI is a questionnaire for informants that consists of 17 instrumental items and 1 basic item (getting dressed) intended to reflect activities of daily living. The total score ranges from 0 to 53, with lower scores indicating greater impairment.

Alzheimer's Disease Composite Score (ADCOMS)

ADCOMS is a weighted linear combination of selected items from 3 commonly used scales: 4 items from the ADAS-Cog, 2 items from the MMSE, and all 6 items from the CDR-SB. ADCOMS scores range from 0 to 1.97 with a higher composite score indicating greater disease severity.

Exploratory Health-Related Quality of Life Assessments

The following health-related quality of life assessments were included as exploratory endpoints:

- European Quality of Life-5 Dimensions 5-Level version (EQ-5D-5L) is a measure of health-related quality of life that covers 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). The assessment was completed by the subject, the care partner as a proxy of the subject, and by the care partner.
- Quality of Life in Alzheimer's Disease (QOL-AD) is an interview with 13 questions specifically interrogating the general quality of life for patients with AD. The assessment was completed by the subject and the care partner as a proxy of the subject.
- The Zarit Burden Interview is a 22-item instrument to specifically assess the challenges experienced by care partners of individuals with AD.

Pharmacodynamic Endpoints

- Change from baseline in tau PET as measured by ^{18}F-MK-6240 PET and quantified by a composite SUVR for the following regions: temporal, medial temporal, meta-temporal, occipital, parietal, cingulate, frontal, and whole cortical gray matter. A measurement of global tau load (Tau^{IQ}) was also assessed.
- Change from baseline in CSF levels of $A\beta_{1-40}$, $A\beta_{1-42}$, phosphorylated tau at residue 181 (p-tau 181), total tau (t-tau), neurofilament light chain (NfL), and neurogranin.
- Change from baseline in plasma levels of $A\beta_{42/40}$, p-tau 181, NfL, and glial fibrillary acidic protein (GFAP).
- Change from baseline in brain volumes as measured by volumetric magnetic resonance imaging (vMRI) for the following regions: total hippocampal, left hippocampal, right hippocampal, whole brain, lateral ventricular, and cortical thickness.

Dosing

Selection of the 10 mg/kg biweekly dosing regimen was based on the results of Study 201.

Dose modifications/discontinuations

Study drug was temporarily interrupted for evidence of symptomatic or radiographically moderate or severe ARIA-E or development of any of the following categories of ARIA-H: a single macrohemorrhage (>10 mm at greater diameter), multiple (>10) cerebral microhemorrhages cumulatively, symptomatic cerebral microhemorrhages, or symptomatic superficial siderosis.

Upon resolution/stabilization of the event, the subject resumed drug treatment for the remainder of the study. If a third event occurred, the subject was discontinued from the study drug. For subjects who paused dosing due to more than 10 cerebral microhemorrhages, study drug was discontinued if further new microhemorrhages developed after resumption of treatment.

Study drug was discontinued if any of the following were observed:

- Infusion or injection of Grade 3 severity or above that did not lessen or resolve with treatment
- Clinical features which indicate meningoencephalitis
- Hypersensitivity reactions with clinical features of tissue injury
- Severe ARIA-E associated with a serious adverse event (SAE)

Statistical Analysis Plan:
The Statistical Analysis Plan (SAP) was issued on April 9, 2019, and was amended once, with the final version implemented on September 6, 2022, prior to study completion.

A mixed model repeated measures (MMRM) model was used to analyze change from baseline in CDR-SB at 18 months with baseline CDR-SB as a covariate and treatment group, visit, clinical subgroup (MCI due to AD or mild AD dementia), use of AD medication at baseline (yes or no), ApoE ε4 carrier status (carrier or non-carrier), geographical region (North America, Europe, or Asia Pacific), baseline CDR-SB-by-visit, and treatment group-by-visit interactions as fixed effects. All observed data were included in the analysis, including data collected after intercurrent events.

Each statistical test was performed at a significance level of two-sided alpha = 0.05. Tests for secondary endpoints were only performed if the preceding test was statistically significant. Key secondary endpoints were tested in the following order: (1) change from baseline in amyloid PET (Centiloids) at 18 months, (2) change from baseline in ADAS-Cog 14 at 18 months, (3) change from baseline in ADCOMS at 18 months, and (4) change from baseline in ADCS-ADL-MCI at 18 months.

The Applicant defined two populations for the primary efficacy analysis depending on the regulatory authority: the ITT Full Analysis Set (FAS+) for European and Japanese regulatory authorities, and the ITT FDA Full Analysis Set (ITT FDA FAS) for the FDA and other global authorities. The FAS+ comprised randomized subjects who received at least one dose of study drug and who had a baseline assessment and at least one post-dose primary efficacy measurement. In an attempt to address potential missed doses due to the COVID-19 pandemic, the FDA FAS was similar to the FAS+, but excluded subjects randomized on or before the end date of the dosing hold at sites which had dosing holds of 6 or more weeks (equal to 3 consecutive doses).

<u>Subgroup Analyses</u>

Subgroup analyses for the clinical and biomarker endpoints were planned for the following subgroups:

- Age group (<65 years, 65-74 years, and ≥75 years)
- Sex (male, female)
- Ethnicity (Hispanic-Latino, not Hispanic-Latino)

- Race (White, Black or African American, Asian, Other)
- Geographical region (North America, Europe, Asia Pacific)
- Clinical subgroup (MCI due to Alzheimer's disease, Mild Alzheimer's disease dementia)
- ApoE ε4 carrier status (carrier, non-carrier)
- ApoE ε4 genotype (homozygous carriers, heterozygous carriers, non-carriers)
- Use of Alzheimer's disease medication at baseline (yes, no)

Results

A total of 5967 subjects were screened for entry into the study and 1795 subjects were randomized. All subjects who were randomized received at least one dose of study drug. A total of 61 subjects received study drug but were not included in the FAS+ population due to missing post-baseline efficacy assessments. The distribution of the reasons for discontinuation between the arms was similar with the exception of more subjects in the lecanemab treatment arm discontinuing treatment or study due to adverse events. Table 1 contains information regarding demographic and disease characteristics for the FAS. Demographic characteristics were balanced across the treatment arms and generally representative of the patient population except for an under-representation of African American patients. Overall, 52% of subjects were enrolled in the United States.

Table 1: Study 301 Baseline Demographic and Disease Characteristics (Full Analysis Set+)

Demographic or Disease Characteristics	Placebo N=875 n(%)	Lecanemab N=859 n(%)	Total N=1734 n(%)
Sex			
Male	411 (47.0%)	416 (48.4%)	827 (47.7%)
Female	464 (53.0%)	443 (51.6%)	907 (52.3%)
Age group			
>=75 years	316 (36.1%)	325 (37.8%)	641 (37.0%)
>=65, <75 years	381 (43.5%)	368 (42.8%)	749 (43.2%)
<65 years	178 (20.3%)	166 (19.3%)	344 (19.8%)
Race			
White	677 (77.4%)	655 (76.3%)	1332 (76.8%)
Black or African American	24 (2.7%)	20 (2.3%)	44 (2.5%)
Asian	148 (16.9%)	147 (17.1%)	295 (17.0%)
Missing	12 (1.4%)	16 (1.9%)	28 (1.6%)
Other	12 (1.4%)	21 (2.4%)	33 (1.9%)
American Indian or Alaskan Native	2 (0.2%)		2 (0.1%)
Ethnicity			
Not Hispanic or Latino	743 (84.9%)	715 (83.2%)	1458 (84.1%)
Hispanic or Latino	108 (12.3%)	107 (12.5%)	215 (12.4%)
Missing	24 (2.7%)	37 (4.3%)	61 (3.5%)
Region			
North America	516 (59.0%)	514 (59.8%)	1030 (59.4%)
Europe	213 (24.3%)	204 (23.7%)	417 (24.0%)
Asia-Pacific	146 (16.7%)	141 (16.4%)	287 (16.6%)

Demographic or Disease Characteristics	Placebo N=875 n(%)	Lecanemab N=859 n(%)	Total N=1734 n(%)
Baseline clinical stage			
MCI	544 (62.2%)	528 (61.5%)	1072 (61.8%)
Mild AD	331 (37.8%)	331 (38.5%)	662 (38.2%)
Laboratory ApoE ε4 status			
Carrier	600 (68.6%)	592 (68.9%)	1192 (68.7%)
Heterozygote	468 (53.3%)	456 (43.1%)	924 (53.3%)
Homozygote	132 (15.1%)	136 (15.8%)	268 (15.5%)
Noncarrier	275 (31.4%)	267 (31.1%)	542 (31.3%)
Baseline CDR global score			
0.5	706 (80.7%)	694 (80.8%)	1400 (80.7%)
1	169 (19.3%)	165 (19.2%)	334 (19.3%)
Baseline MMSE			
Mean (SD)	25.6 (2.2)	25.5 (2.2)	25.6 (2.2)
Median (min, max)	25.0 (22.0, 30.0)	25.0 (22.0, 30.0)	25.0 (22.0, 30.0)

Source: adsl.xpt (created by reviewer)

Primary Endpoint

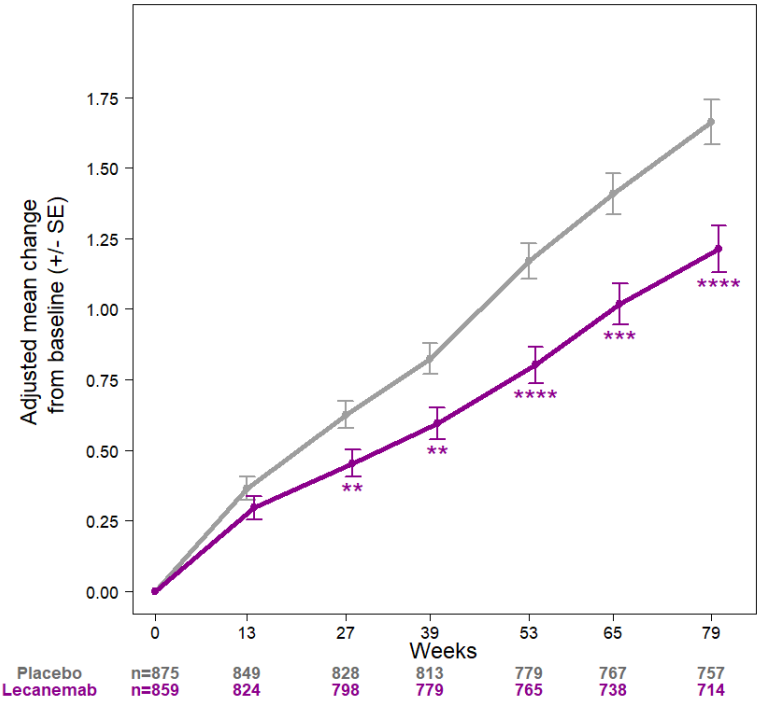
The primary efficacy endpoint analysis, change from baseline in CDR-SB at Week 79, demonstrated a statistically significant treatment effect in the lecanemab treatment arm compared to placebo in the FAS+ population (-0.45[-27%], p=0.00005) (Table 2) and the FDA FAS population (-0.39[-25%], p=0.0004). Nominal statistical significance was reached by Week 27 and maintained through Week 79 (Figure 1).

Table 2: Primary Endpoint Analysis, FAS+ Population, Study 301

Parameter	Placebo (N=875)	Lecanemab (N=859)
Baseline CDR-SB		
n	875	859
Mean	3.22	3.17
Change from baseline in CDR-SB at Week 79		
n	757	714
Adjusted mean	1.663	1.213
Standard error	0.080	0.082
Difference from placebo		-0.451
95% CI for difference		(-0.669, -0.233)
% difference vs. placebo		-27%
p-value (compared with placebo)		0.00005

Source: Table 14.2.1.1.1 and 14.2.1.1.1 in Study 301 CSR
Abbreviations: CDR-SB, Clinical Dementia Rating-Sum of Boxes; CI, confidence interval; FAS+, full analysis set

Figure 1: Longitudinal Change From Baseline for CDR-SB, FAS+ Population, Study 301



Source: Tables 14.2.1.1.1 and 14.2.1.1.2 in Study 301 CSR
*p<0.05, **p<0.01, ***p<0.001, ****p<0.0001
Abbreviations: CDR-SB, Clinical Dementia Rating-Sum of Boxes; FAS+, full analysis set

In the overall population, 5.7% of subjects were on an AD symptomatic medication but did not remain on a stable dose during the study, with similar rates seen for placebo (6.2%) and lecanemab (5.2%). In the overall population, 7.3% of subjects started a new AD symptomatic medication regardless of use at baseline, which was similar for placebo (7.5%) and lecanemab (7.1%). Tipping point sensitivity analyses for missing data based on multiple imputations using shift parameters (delta) for informative missingness, separately for each treatment group for generating outcomes for missing data, were prespecified and performed. Tipping point sensitivity analyses by adding the shift parameter (delta) (e.g., 1.0, 1.5) to only lecanemab Week 79 imputed missing CDR-SB outcomes show how the p-value of the primary analysis changes under informative missingness scenarios for lecanemab. The deltas that will overturn the primary analysis were not plausible; thus, the primary analysis results were robust to plausible departures from the missingness assumption underlying the primary results.

Several other prespecified sensitivity analyses demonstrated that the statistically significant results were robust to different analysis populations and assumptions. A sensitivity analysis using log-transformed data demonstrated that the primary analysis results were not sensitive to departures from normality, including presence of rapid progressors. To address the potential effect of functional unblinding due to ARIA or infusion reactions, the results of the primary analysis were compared to a similar analysis using a reduced dataset in which all

assessments after occurrence of ARIA (ARIA-E or ARIA-H) or infusion reaction were excluded. A definitive conclusion cannot be reached by such an analysis due to the lack of a balanced control group, including balance with respect to follow-up time, but the results do not appear to suggest a systematic bias due to functional unblinding. It is also worth noting that steps were taken in the protocol to minimize functional unblinding, specifically the use of an independent rater who was blinded to the subject's evaluations, including imaging results. Also, ARIA and infusion reactions occurred in the placebo arm, suggesting that investigators could not, with complete accuracy, know the subject's treatment group based on occurrence of an ARIA event.

Secondary Endpoints

Statistically significant results favoring lecanemab were observed for all multiplicity-controlled secondary endpoints.

Lecanemab treatment demonstrated a statistically significant treatment effect on change from baseline in brain amyloid as measured by PET and reported as Centiloids at Week 79 (-59.1, p<0.00001) (Table 3). The results indicate a time-dependent relationship.

Table 3: Pharmacodynamic Endpoint Analysis (Amyloid PET), Study 301

Parameter	Placebo (N=353)	Lecanemab (N=363)
Baseline centiloid		
n	351	360
Mean	75.0	77.9
Change from baseline in centiloid at Week 79		
n	205	210
Adjusted mean	3.64	-55.5
Standard error	1.47	1.46
Difference from placebo		-59.1
95% CI for difference		(-62.6, -55.6)
p-value (compared with placebo)		<0.00001

Source: Tables 14.2.2.1.1 and 14.2.2.1.2 in Study 301 CSR
Abbreviations: CI, confidence interval; PET, positron emission tomography

Lecanemab treatment resulted in a reduction in change from baseline as measured on the ADAS-Cog 14 (-1.442[-26%], p=0.00065), ADCS-ADL-MCI (2.016[-37%], p<0.00001), and ADCOMS (-0.050[-24%], p=0.00002) as compared to placebo. Statistically significant results of similar magnitude were observed using the FDA FAS analyses set. Results were robust across sensitivity analyses. Nominal statistical significance was reached by Week 27 and maintained through Week 79 for all secondary clinical endpoints.

Table 4: Secondary Clinical Endpoint Analysis, Week 79, FAS+ Population, Study 301

	Placebo Decline (N=875)		Lecanemab (N=859)		
Secondary Endpoint	n	Adjusted Mean	n	Difference vs. Placebo (%)	p-Value
ADAS-Cog 14	738	5.581	703	-1.442 (-26%)	p=0.00065
ADCS-ADL-MCI	796	-5.500	676	2.016 (-37%)	p<0.00001
ADCOMS	749	0.214	708	-0.50 (-24%)	p=0.00002

Source: Tables 14.2.2.2.2, 14.2.2.3.2, and 14.2.2.4.2 in Study 301 CSR
Abbreviations: ADAS-Cog 14, 14-item Alzheimer's Disease Assessment Scale - Cognitive Subscale; ADCOMS, Alzheimer's Disease Composite Score; ADCS-ADL-MCI, Alzheimer's Disease Cooperative Study - Activities of Daily Living Scale for use in Mild Cognitive Impairment; FAS+, full analysis set

Subgroup Analyses

Prespecified subgroup analyses were performed across demographic and baseline characteristics. Treatment comparisons favored lecanemab in all subgroups across the 3 distinct clinical endpoints, except for change from baseline in CDR-SB in ApoE ε4 homozygous subjects. It is worth noting that the ApoE ε4 homozygous subgroup is one of the smallest prespecified subgroups with 132 and 136 subjects in the placebo and lecanemab arms, respectively. Also, results for ADAS-Cog 14 and ADCS-ADL-MCI favor lecanemab in this subgroup. Discordant results between CDR-SB and ADAS-Cog 14 and ADCS-ADL-MCI have been observed in other studies. Similarly, results for health outcome measures and biomarkers in homozygous carriers are consistent with the overall results in the population and support a treatment effect. Finally, a diminished treatment response in ApoE ε4 carriers relative to noncarriers has not been a consistent finding across trials of other anti-amyloid therapies in the class.

Exploratory Health-Related Quality of Life Assessments

Lecanemab treatment was associated with a reduction in decline in the EQ-5D-5L Health Today score by subject and QOL-AD total score by subject and care partner as proxy, and a reduction in the increase of the Zarit Burden Interview total score at Week 79 compared to placebo. No treatment effect was observed for the EQ-5D-5L by care partner or by care partner as proxy.

Pharmacodynamic Endpoints

Tau PET was evaluated in 257 subjects (122 in the placebo arm and 135 in the lecanemab treatment arm). Regional analyses of tau PET suggested a smaller change from baseline in the lecanemab treatment arm compared to placebo with nominal statistical significance achieved for the temporal, medial temporal, and meta-temporal regions. Global tau load computed from the Tau IQ algorithm showed no statistically significant treatment difference.

Lecanemab treatment was associated with a decrease in whole brain volume and cortical thickness and an increase in ventricular volume at Week 79. Decreases in brain volume have been observed with other monoclonal antibodies that target amyloid. Although decreases in brain volume can reflect atrophy or neurodegeneration, the physiologic or pathologic changes that underly the observed changes in brain volume with monoclonal antibodies

targeting amyloid are unclear. Change in brain volume is a nonspecific finding that could reflect a number of different underlying physiologic processes related to amyloid removal. Fluid biomarkers of neurodegeneration, including plasma NfL, in Study 301, do not suggest a greater extent of neurodegeneration with lecanemab treatment. It is also notable that, in contrast to the whole brain and ventricular volume changes, lecanemab treatment was associated with a reduction in loss of total hippocampal volume. The clinical relevance of the observed changes in whole brain and ventricular volumes are unclear, particularly in light of the favorable results on clinical endpoints observed in Study 301. It will be important to collect longer-term data in a large number of subjects to further understand the clinical implications, if any, of these observations.

Lecanemab treatment was associated with an increase in plasma $A\beta_{42/40}$ and a decrease in plasma p-tau 181 and plasma GFAP compared to placebo at Week 77.
Lecanemab treatment was also associated with an increase in CSF $A\beta_{1-42}$ and a decrease in CSF p-tau 181, t-tau, and neurogranin as compared to placebo at Week 77.

Biostatistics Review Conclusions

Dr. Massie concludes that Study 301 appears to confirm the clinical benefit of lecanemab based on highly statistically significant results on the primary endpoint and multiplicity-controlled key secondary endpoints. The results appear reasonably robust to missing data based on tipping point analysis and other sensitivity analyses. For the homozygous ApoE ε4 carrier subgroup, the review concludes that there is insufficient evidence of a qualitative interaction but a quantitative interaction, i.e., a smaller effect but still favoring lecanemab, may be plausible. Lastly, the review notes limitations with the secondary analysis that suggested the preservation of CDR-SB of approximately 5.3 months relative to placebo, and notes that this analysis should not be overinterpreted or emphasized without considering these limitations.

Efficacy Conclusions

Lecanemab received accelerated approval based on data from Study 201 that demonstrated substantial evidence of effectiveness on a reasonably likely surrogate endpoint, reduction in brain amyloid beta plaques as measured by PET imaging. In this BLA supplement, the Applicant is seeking traditional approval of lecanemab based on efficacy, safety, and biomarker data from Study 301, a randomized, double-blind, placebo-controlled Phase 3 study in patients with MCI due to Alzheimer's disease or mild Alzheimer's disease dementia. Study 301 is intended to satisfy postmarketing requirement 4384-1 to verify the clinical benefit of lecanemab.

Study 301 demonstrated consistent and robust clinical benefit on all primary and secondary endpoints. The primary efficacy endpoint analysis, change from baseline in CDR-SB at Week 79, demonstrated a statistically significant treatment effect in the lecanemab treatment arm compared to placebo in the FAS+ population (-0.45[-27%], p=0.00005 and the FDA FAS population (-0.39[-25%], p=0.0004). Nominal statistical significance was reached by Week 27

and maintained through Week 79. Results were robust across sensitivity analyses. Statistically significant results favoring lecanemab were observed for all 3 multiplicity-controlled secondary clinical endpoints. Lecanemab resulted in a reduction in change from baseline as measured on the ADAS-Cog 14 (-1.442[-26%], p=0.00065), ADCS-ADL-MCI (2.016[-37%], p<0.00001), and ADCOMS (-0.050[-24%], p=0.00002) as compared to placebo. Amyloid PET was assessed in 40% of the overall population (353 subjects in the placebo arm and 363 subjects in the lecanemab treatment arm). Lecanemab treatment demonstrated a statistically significant treatment effect on change from baseline in brain amyloid as measured by PET and reported as Centiloids at Week 79 (-59.1, p<0.00001).

It is noted that an exploratory subgroup analysis in ApoE ε4 homozygotes showed no clinical benefit on the CDR-SB; however, there were trends for efficacy on the ADAS-Cog 14 and ADCS-ADL-MCI scale that were lower than heterozygotes and non-carriers. There were favorable trends for treatment effects in health-related outcome measures and biomarkers in the homozygote subgroup. Dr. Krudys notes that the ApoE ε4 homozygous subgroup is a small subgroup that is not powered to detect treatment effects. Additionally, there is no mechanistic reason to expect a differential effect in benefit between genotype status, and such effects have not been observed consistently in other studies. The secondary and exploratory endpoints support a benefit in this population. Overall, the data appear to suggest a treatment benefit for lecanemab in ApoE ε4 homozygotes although there are uncertainties about the magnitude of benefit in this subgroup relative to heterozygotes and noncarriers. This issue was also discussed at the advisory committee meeting and the panelists noted that the data in this subgroup is limited in interpretability do to the small sample size and exploratory nature of the analysis. The consensus from the advisory committee was that the benefit-risk assessment remained favorable in the ApoE ε4 homozygous population.

In addition to being statistically robust and persuasive, the results on the clinical endpoints appear to be clinically meaningful. The primary endpoint of Study 301, the Clinical Dementia Rating Scale-sum of boxes or CDR-SB, is considered to be an inherently clinically meaningful scale, in that a change on any individual domain on that scale represents a meaningful change in function for the patient. The scale consists of 6 domains that assess cognition and function that are scored from 0 to 3, for a total scoring range of 0 to 18. The scoring is based on decline from the patient's previous usual level of function due to cognitive loss, and not from impairment due to other factors such as medical comorbidities. For the CDR-SB, the minimal amount of change that can be scored in a domain is 0.5, which would be from 0 to 0.5, which indicates progression from no impairment to slight impairment, or from 0.5 to 1, which indicates progression from slight impairment to mild impairment. These 0.5 increments measure changes in cognition and function that are noticeable and meaningful to patients and their caregivers.

When considering the CDR-SB results on Study 301, it is very important to distinguish between clinically important individual-level change and group-level change on the scale. On an individual level, we consider the smallest incremental score change on the CDR-SB of 0.5

to be clinically meaningful. We see that at the group-level, the mean difference in Study 301 is approximately 0.5. That means that subjects treated with lecanemab had, on average, a half point less decline on the CDR-SB compared to subjects who received placebo. On an individual level some subjects treated with lecanemab had greater response and some had less, but overall, there were more individuals in the lecanemab group that had less decline on the CDR-SB of at least 0.5 points compared to placebo, and this difference was statistically significant. It is anticipated that the treatment benefit from a drug that impacts underlying disease biology will increase over time and that is, in fact, what is demonstrated in Study 301.

When considering clinical meaningfulness, we also look to support from secondary endpoints. In this situation, we see clear and consistent findings of efficacy on clinically relevant assessments, the ADAS-Cog 14, a measure of cognition, and the ADCS-ADL-MCI, a measure of activities of daily living, as well as support from health-related quality of life measures.

A slope analysis that suggests that at the 18-month time point, subjects treated with lecanemab were delayed by approximately 5 months from reaching a similar level of decline as the placebo group. Dr. Massie notes limitations in the interpretability of this time estimate; however, the concept of "saving time" is a potentially useful way to consider the effects of a therapy that targets the underlying pathophysiology of a neurodegenerative disease. A delay in disease progression means that subjects will prolong the time spent in an earlier stage of the disease where they have greater function and independence, and this is undoubtedly clinically meaningful to patients. Overall, the data provide a compelling case for a clinically meaningful effect of lecanemab in patients with Alzheimer's disease.

The clinical reviewer, Dr. Krudys, has concluded that the results of Study 301 confirms the clinical benefit of lecanemab for the treatment of Alzheimer's disease and he recommends traditional approval. The clinical pharmacology review team also supports traditional approval of the application. The statistical review team also concludes that Study 301 confirms the clinical benefit of lecanemab.

The results of Study 301 verify and describe the clinical benefit of lecanemab for the treatment of Alzheimer's disease. The collective evidence from Study 201 and 301 continue to demonstrate substantial evidence of effectiveness for lecanemab for the treatment of Alzheimer's disease, and support the traditional approval of lecanemab in this population. Study 301 is also adequate to satisfy postmarketing requirement 4384-1 to verify the clinical benefit of lecanemab. The effect on the primary endpoint represents a clinically meaningful reduction of clinical decline. The finding on the primary endpoint is supported by statistically significant results for all 4 multiplicity-controlled secondary endpoints, including endpoints capturing distinct information regarding cognitive decline. The treatment effect in Study 301 is supported by the consistently favorable results for the primary and secondary endpoints across subgroups of interest defined by demographic and baseline disease characteristics. Biomarkers reflecting target engagement, effects on downstream tau pathophysiology, and neurodegeneration support the observations on the clinical endpoints.

As previously discussed in the initial review of lecanemab for accelerated approval, lecanemab will be indicated for the treatment of Alzheimer's disease; however, the indication statement will note that treatment should be initiated in patients with mild cognitive impairment or mild dementia stage of disease, the population in which treatment was initiated in clinical trials, and that there are no safety or effectiveness data on initiating treatment at earlier or later stages of the disease than were studied. It is appropriate to indicate the drug for Alzheimer's disease because the disease exists on a spectrum and there may not be clear distinctions between one stage and another. For example, a patient does not change from mild to moderate dementia at a discrete timepoint, but there is a slow progression of the disease with overlying waxing and waning of cognitive and behavioral symptoms. Therefore, it will require clinical judgement by the prescriber regarding whether a patient is at an appropriate stage of disease for treatment and if there is a suggestion of clinical benefit that may warrant continued treatment despite progression of the disease.

7. Safety

Dr. Deniz Erten-Lyons performed the safety review for the submission with CDTL, Dr. Ranjit Mani, and Deputy Director for Safety, Dr. Sally Yasuda.

Exposures and Adequacy of the Safety Database

The primary safety data are from Study 301 Core and its open label extension (301 OLE). Ongoing Study 201 OLE provides supportive safety data for up to 18 months of exposure at the dose of 10 mg/kg biweekly, and ongoing studies 301 Core (China), 303 and Dian-TU that include subjects with preclinical AD and a different dosing schedule than that for the proposed indication provide blinded safety information. Study 201 Core was reviewed in the original submission and primarily contributes in the present review to total exposure.

The safety database includes 2345 subjects exposed to at least one dose of lecanemab at any dose, and 2090 exposed to at least 1 dose of lecanemab 10 mg/kg, including 898 in 301 Core and 714 in 301 OLE (1612 total in 301 Core and OLE) on lecanemab 10 mg/kg biweekly. Across the development program, at the proposed dose of 10 mg/kg biweekly, 1604 subjects were treated for at least 6 months, 1261 for at least 12 months, and 965 for at least 18 months, as of the 90 day safety update. In 301 Core, 816 subjects were exposed to lecanemab for at least 6 months, 765 for at least 12 months, and 698 for at least 18 months. The ICH guidelines for drugs intended for long-term use of at least 300 subjects for 6 months and 100 subjects for 1 year at the clinically relevant dose are met. The safety database is adequate to assess the safety of lecanemab 10 mg/kg biweekly.

In Study 301 Core, 60% of the population treated with lecanemab in the safety analysis set were from North America. The mean age was approximately 71 years (range 50 to 90 years).

Eighty percent (n=723) were older than 65 years old and 38% (n=340) were at least 75 years old. Fifty-one percent were women. Sixteen percent (141/898) of subjects were ApoE ε4 homozygotes, 53% (479/898) were heterozygotes, and 31% (278/898) were noncarriers; Dr. Erten-Lyons notes that this is representative of the general population of patients with Alzheimer's disease. White subjects accounted for 76%, Hispanic or Latino accounted for 13%, 17% were Asian, and Black or African American accounted for 2%. The population demographics were similar for lecanemab and placebo. Dr. Erten-Lyons notes that Black subjects are under-represented compared to the general United States population but that they are at increased risk for Alzheimer's disease. In addition, Dr. Erten-Lyons notes that patients with moderate or severe dementia due to Alzheimer's disease were not eligible for enrollment. Therefore, the safety outcomes may underestimate the impact of adverse events in a broader population.

Dr. Erten-Lyons did not identify substantive quality issues in the submission that would impact data analysis and safety review.

Deaths

In the review of the original BLA submission, Dr. Erten-Lyons did not identify any deaths attributable to treatment with lecanemab in 201 Core or in the OLE. She notes that in the placebo-controlled 301 Core study, there was not an excess of deaths in the lecanemab group (0.7%, 6/898) compared to placebo (0.8%, 7/897) for deaths for which the precipitating event occurred within 30 days after the last dose of study drug. One additional death each in lecanemab (diabetic ketoacidosis) and in placebo (cardiopulmonary arrest) occurred beyond 30 days after the last dose of study drug. In 301 Core, a role for lecanemab in the deaths is not apparent, there is no unusual cluster of deaths, and none of the deaths was preceded by ARIA.

In 301 OLE the incidence of deaths was 0.7% (9/1385). In 5 of the deaths (myocardial infarction in a subject with risk factors, acute cardiac failure in a subject who had received multiple doses with no previous drug-related adverse events, fatal car accident, 2 deaths in subjects with Covid 19), Dr. Erten-Lyons could not identify a clear role of study drug. In addition, there was insufficient information to make a causality assessment in one subject who presented 9 days after the 9th dose of lecanemab with dysarthria and a 2-day history of diarrhea, with a blood pressure of 180/100 mm Hg, whose death was reportedly due to cardiorespiratory arrest and suspected cerebral vascular accident ((b) (6)

In 301 OLE there were 3 notable deaths, as follows, for which a role for lecanemab cannot be ruled out.

Subject (b) (6), whose death was noted in the review of the original BLA and includes updated information in the present submission, was an 88-year-old male, ApoE ε4 noncarrier, with a past medical history including atrial fibrillation, aortic stenosis, aortic valve replacement, hyperlipidemia, coronary artery disease and bypass surgery, and lacunar stroke.

He was randomized to placebo in 301 Core. He had 3 microhemorrhages at baseline (right cerebellum, left occipital region, left frontal region). Baseline medications at the time of starting 301 OLE included donepezil, apixaban, tamsulosin, and atorvastatin. The subject sustained a fall on Day 77 after 6 doses of study drug, followed by COVID-19 on Day 98 (treated with "protease inhibitors 150/100 mg/mg PO QD" for 5 days), an ulnar pseudoaneurysm treated with thrombin on Day 108, and another fall from bed on Day 114. At the study visit on Day 116 the subject reported increased confusion. Lecanemab was not administered due to multiple medical concerns including past events of recurrent falls, COVID-19, and pneumonia. MRI on Day 118 showed a left occipital cerebral hemorrhage (> 1 cm) with ARIA-E in the left occipital area and a new ARIA-H microhemorrhage in the left frontal area. Apixiban was stopped. The last dose of lecanemab had been on Day 98 and was discontinued because of cerebral hemorrhage. The subject had a myocardial infarction on Day 124 and Plavix (clopidogrel) was started. The subject had TIA-like events on Day 128. The subject enrolled in hospice and was continued Plavix (clopidogrel) as well as lorazepam for comfort. The subject died on Day 144. Brain autopsy did not show amyloid in the vicinity of the hemorrhage; however, minimal to mild amyloid angiopathy was noted on immunohistochemical staining in the left occipital cortex with no obvious plaque deposition. Cerebral hemorrhage and ARIA-E were co-localized, which could suggest that cerebral hemorrhage was related to lecanemab. However, falls and anticoagulation are confounders in the event of cerebral hemorrhage, with an increased risk of cerebral hemorrhage in subjects treated with anticoagulants on lecanemab (please refer to the section on ARIA and antithrombotic therapy in this document). The autopsy report did not provide a cause of death. As Dr. Erten-Lyons notes, the role of ARIA-H, ARIA-E and cerebral hemorrhage in the subject's death is unclear, given the concurrent medical events in a subject with atrial fibrillation off of anticoagulation, and subject's decision to not pursue any aggressive medical treatment and transition to hospice.

Subject (b) (6) was a 65-year-old woman with MCI, homozygous for ApoE ε4, who completed 301 Core on placebo and enrolled in 301 OLE. At the screening MRI prior to the Extension Phase, she did not have any ARIA-E, microhemorrhages, or superficial siderosis. Relevant past medical history was patent foramen ovale. Based on the adverse event dataset, she complained about headaches after each dose of lecanemab in the open-label extension phase. On Extension Day 33, four days after the third dose of lecanemab, the subject was noted to have a blank stare, talking incoherently with garbled speech, and was taken to an emergency room. A CT of the head diagnosed a left-sided ischemic stroke due to an LM3 occlusion. After administration of the thrombolytic medication tissue plasminogen activator (tPA) the subject experienced a headache and agitation and imaging showed bilateral intracerebral hemorrhage with subarachnoid hemorrhage and EEG showed seizure activity. The tPA was stopped and cryoprecipitate and tranexamic acid were given for reversal of tPA. She was treated with Haldol for agitation and lorazepam and Keppra for seizures. Her blood pressure was greater than 200 mmHg, for which she was started on nicardipine infusion. Her encephalopathy worsened and she was intubated. Brain MRI obtained on hospital day 3 showed extensive multicompartmental intracerebral hemorrhages, innumerable hematomas, subarachnoid hemorrhage and right intraventricular hemorrhage

with 5 mm leftward midline shift and bilateral uncal herniation. According to the clinical history provided in the autopsy report this MRI also showed an acute right thalamocapsular infarct. She was extubated and died eight days after the last dose of study drug. A subsequent autopsy reported cause of death as nontraumatic intracerebral hemorrhage. Dr. Erten-Lyons notes that the autopsy showed extensive multifocal intraparenchymal hemorrhages, Alzheimer's disease neuropathologic changes, histiocytic/microglial reaction to parenchymal amyloid plaques, cerebral amyloid angiopathy with diffuse histiocytic vasculitis and focal fibrinoid necrosis. Vasculopathy was described as involving amyloid deposition within (but not outside) the blood vessel walls. The autopsy report states that moderate cerebral amyloid angiopathy was identified throughout by immunohistochemical staining, and also notes that fragmented cerebral amyloid angiopathy is present in areas involved by histiocytic vasculitis. There was no vascular territory infarct apart from an agonal lesion in the right posterior limb of the internal capsule which was felt to correspond to the acute right thalamocapsular infarct observed on MRI prior to death, and which was consistent with a small focus of agonal ischemia, unassociated with vasculitis or CAA. Although, as Dr. Erten-Lyons notes, the subject's screening MRI did not suggest underlying cerebral amyloid angiopathy (CAA), up to 90% of individuals with pathologic AD also have evidence of CAA pathology, but many show no imaging findings consistent with CAA.[1,2,3,4] Dr. Erten-Lyons notes that thrombolysis and cerebral amyloid angiopathy are associated with an increased risk of intracerebral hemorrhage which confound the ability to draw any conclusions on causality; however, she cannot completely rule out a role of lecanemab in this event. In addition, whether the necrotizing vasculitis is a manifestation of CAA related inflammation (CAA-ri/vasculitis) or whether study drug directly played a role in the event of vasculitis is not known. Dr. Erton-Lyons notes that subject (b) (6) described below, had similar autopsy findings, leading to a concern that lecanemab may enhance an inflammatory reaction manifesting similar to CAA-re/vasculitis in subjects with underlying severe CAA.

Subject (b) (6) was a 79 year old ApoE ε4 homozygote with underlying CAA, who was randomized to placebo in 301 Core. The details of this case have been reported in a pre-print

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[1] Love S, Miners S, Palmer J, Chalmers K, Kehoe P. Insights into the pathogenesis and pathogenicity of cerebral amyloid angiopathy. Frontiers in Bioscience 14, 4778-4792, January 1, 2009.

[2] Yu L, Boyle PA, Nag S, Leurgans S, Buchman AS, Wilson RS, Arvanitakis Z, Farfel JM, De Jager PL, Bennett DA, Schneider JA. APOE and Cerebral Amyloid Angiopathy in Community Dwelling Older Persons. Neurobiol Aging. 2015 November; 36(11): 2946–2953. doi:10.1016/j.neurobiolaging.2015.08.008.

[3] Jäkel L, De Kort AM, Klijn CJM, Schreuder FHBM, Verbeek MM. Prevalence of cerebral amyloid angiopathy: A systematic review and meta-analysis. Alzheimers Dement. 2022 Jan;18(1):10-28. doi: 10.1002/alz.12366. Epub 2021 May 31.

[4]Brenowitz WD, Nelson PT, Besser LM, Heller KB, Kukull WA. Cerebral amyloid angiopathy and its co-occurrence with Alzheimer's disease and other cerebrovascular neuropathlogic changes. Neurobiol Aging 2015; 36 (2702-2708). doi:10.1016/j.neurobiolaging.2015.06.028.

manuscript[5] that has not been peer-reviewed. According to the narrative provided by the Applicant, the screening MRI prior to enrollment in 301 Core only showed a left parietal meningioma < 1cm, and no microhemorrhages. According to the pre-print manuscript, the pre-treatment MRI before the open-label extension showed 4 small cerebral microhemorrhages. The Agency reviewed the pre-treatment MRI and confirms at least 3 cerebral hemorrhages present before the open-label extension. Her relevant past medical history included chronic kidney disease, aortic atherosclerosis, hyperlipidemia. She had the third dose of lecanemab on Extension Day 31. Based on the pre-print manuscript and hospital records, the subject had been complaining of headaches occurring about an hour after each infusion. After the third dose of lecanemab, she began to experience progressively worsening memory impairment described as "brain fog." One week after the third dose of lecanemab, the subject experienced a sudden onset of difficulty speaking, left head and gaze deviation, and left side weakness, reported in the original CIOMS report as a possible cerebrovascular accident and possible seizure. The manuscript described the event as a seizure, after which she regained alertness but was not communicative or with purposeful interactions. She was sedated and intubated and admitted to the hospital. CT of the brain showed no intracranial hemorrhage, mass effect, or midline shift. She was noted to be in paroxysmal atrial fibrillation. She was evaluated for acute stroke but felt to not be a good candidate for tPA. According to the manuscript, MRI showed multifocal cerebral edema and more than 30 microhemorrhages. The neuroimaging findings were consistent with ARIA. According to an updated CIOMS report provided by the Sponsor on May 18, 2023, the study central MRI reader identified severe ARIA-E and 51 microhemorrhages without macrohemorrhage, midline shift, mass effect, or herniation on the post-treatment hospital MRI. The Agency was able to confirm the presence of cerebral edema consistent with ARIA-E and increased ARIA-H microhemorrhages on the hospital post-treatment MRI. The subject was treated with solumedrol for 3 days for suspected ARIA. Suspected aspiration pneumonia and respiratory distress were reported in the narrative. The manuscript states that an aspiration event led to sepsis with multiorgan failure, and the subject died 5 days after hospital admission. The autopsy report, as reviewed by the Agency, identifies the cause of death as atherosclerotic and hypertensive heart disease with bronchopneumonia with diffuse alveolar damage contributing. The report describes severe amyloid angiopathy with features suggestive of CAA-related inflammation/vasculitis, similar to the autopsy findings of the subject described above.

Cerebral amyloid angiopathy (CAA) is characterized by accumulation of amyloid in the vascular wall. A study of the Uniform Data Set of the National Institute on Aging-funded Alzheimer's Disease Center system that aimed to identify clinical factors associated with the presence of severe CAA in subjects with pathologically confirmed Alzheimer's disease found that approximately 73% of ApoE ε4 homozygotes in the study population had severe CAA

[5] Solopova E, Romero-Fernandez W, Harmsen H, Ventura-Antunes L, Wang E, Shostak A, Maldonado J, Donahue M, Schultz D, Coyne T, Charidimou A, Schrag M. Fatal Iatrogenic Cerebral Amyloid-Related Encephalitis in a patient treated with lecanemab for Alzheimer's disease: neuroimaging and neuropathology. medRxiv 2023.04.26.23289061; doi: https://doi.org/10.1101/2023.04.26.23289061

compared to approximately 27% that had no CAA, and subjects with CAA were more likely to have intracerebral hemorrhage than subjects without CAA (9.3% vs 3.5%).[6]
There were 2 deaths on lecanemab in the setting of intracerebral hemorrhage that occurred in Apo E ε4 homozygous subjects with underlying severe CAA; however, one death had confounding circumstances of tPA administration and source documents have not been provided to corroborate details in the other. Therefore, a potential role for an interaction between lecanemab and underlying severe CAA or CAA-related inflammation/vasculitis cannot be determined. Additionally, these two fatalities occurred in the OLE with no comparator control group. There is high background prevalence of CAA in patients with Alzheimer's disease, as noted above, but there is a lack of definitive clinical criteria for diagnosing CAA. This results in an inability to compare the risk of cerebral hemorrhage in lecanemab-treated subjects with or without CAA, and leads to substantial uncertainty, thus limiting the ability to make any recommendations regarding the use of lecanemab in patients with CAA. Of note, postmarketing pharmacovigilance for vasculitis was requested upon the accelerated approval of lecanemab.

Dr. Erten-Lyons notes that the incidence of death by person-years of exposure to lecanemab in 301 Core and OLE is 6.9/1,000 person years (16/2331.2 person years), including the non-treatment emergent death in 301 Core, and does not exceed the reported incidence from Alzheimer's disease in the US of 133.8/1,000 person years. As Dr. Erton-Lyons notes, this comparison is limited by comparing the population with early-stage Alzheimer's disease (mild cognitive impairment and mild dementia) with the overall Alzheimer's disease population inclusive of later stages.

Serious and Significant Adverse Events

Serious adverse events (SAEs) reported in Study 301 Core and OLE and the ongoing 201 OLE were consistent with those reported in the original submission. In the placebo-controlled Study 301 Core, SAEs occurred in 14% (126/898) of lecanemab-treated subjects and in 11% (101/897) of placebo-treated subjects. The most frequently reported SAEs in 2 or more subjects receiving lecanemab and greater than placebo were infusion-related reactions (1.2% vs 0), ARIA-E (0.8% vs 0), syncope (0.7% vs 0.2%), atrial fibrillation (0.7 vs 0.3 %), and angina pectoris (0.7% vs 0). SAEs of cerebral hemorrhage occurred in 0.3% on lecanemab vs 0 on placebo. ARIA, cerebral hemorrhage, and infusion-related reactions will be discussed as adverse events of special interest.

In 301 OLE, SAEs occurred in 9% (126 /1385) of subjects. Similar to the 301 Core period, the most frequent SAEs in lecanemab treated subjects in 301 OLE were ARIA-E (0.8%), and infusion-related reactions (0.7%). Dr. Erten-Lyons identified the following designated medical events, not discussed elsewhere, that in each case had risk factors for the event: acute

[6] Ringman JM, Sachs MC< Zhou Y. Angiopathy and influence of *APOE* Genotype in Persons with Pathologically Verified Alzheimer Disease. JAMA Neurol 2014; 71:878-883. doi:10.1001/jamaneurol.2014.681

respiratory failure/respiratory failure ((b) (6)), rhabdomyolysis (b) (6), motor neuron disease (b) (6)), and acute kidney injury ((b) (6)).

Dr. Erten-Lyons shows that most TEAEs in 301 Core were mild or moderate in severity based on impact on normal daily activity, with approximately 7% considered severe in both the lecanemab and placebo arms; that was true as well as in 301 OLE, with approximately 5% of subjects having a severe TEAE. The most frequent severe TEAEs (incapacitating, with inability to work or perform normal daily activity) in the lecanemab group in 301 Core were infusion-related reactions, which occurred in 0.8% on lecanemab and none in placebo, fall, which occurred in 0.4% on lecanemab and 0.2% on placebo, and ARIA-E, which occurred in 3 (0.3%) subjects on lecanemab and none in placebo. We note that clinical symptom severity of ARIA TEAEs as characterized in this manner is not the same as the radiographic severity characterization of ARIA events. Both symptom severity and radiographic severity are described in the labeling for ARIA-E and are used to manage treatment with lecanemab.

Discontinuations Due to Adverse Events

In 301 Core, 21% of subjects receiving lecanemab withdrew from the study compared to 16% on placebo. Adverse events leading to study withdrawal occurred in 6% of subjects on lecanemab vs 3% on placebo. In 301 Core, 22% of subjects receiving the study drug discontinued lecanemab compared to 17% on placebo. Adverse events leading to study drug discontinuation occurred in approximately 7% of subjects on lecanemab compared to 3% on placebo. The most frequent events resulting in lecanemab discontinuation and at greater frequency than placebo in 301 Core were ARIA-H (1.7% in lecanemab vs 0.1% in placebo), ARIA-E (1.6% in lecanemab vs 0 in placebo), and infusion-related reactions (1.3% in lecanemab vs 0.1% in placebo).

In 301 OLE, 57/1385 (4.1%) subjects discontinued due to adverse events. The most common reasons for study drug discontinuation in 301 OLE were similar to 301 Core and included ARIA-E, ARIA-H, and infusion-related reactions. There were no new discontinuations due to adverse events reported in ongoing 201 OLE since the review of the original submission.

Treatment-Emergent Adverse Events (TEAEs) of All Severities

The incidence of TEAEs in 301 Core was 89% in the lecanemab arm and 82% in the placebo arm. The most frequently reported TEAEs in 301 on lecanemab were infusion-related reaction, ARIA-H, ARIA-E, and headache (see Table 5). Of note, these TEAEs do not include TEAEs associated with events of ARIA.

Table 5 : Adverse Reactions Reported in at Least 5% of Subjects Treated with Lecanemab and at least 2% greater than Placebo in 301 Core

Dictionary Derived Term	Placebo N=897 N (%)	LEC10-BW N=898 N (%)
Infusion related reaction	64 (7)	236 (26)
Amyloid related imaging abnormality-microhemorrhages	69 (8)[a]	126 (14)
Amyloid related imaging abnormality-edema/effusion	15 (2)	113 (13)
Headache	73 (8)	101 (11)
Superficial siderosis of central nervous system	22 (2)	50 (6)
Rash MQG[a]	37 (4)	52 (6)
Nausea and vomiting	37 (4)	50 (6)

Source: adae.xpt (created by clinical analyst)

[a] ARIA-H includes 1 subject in whom Investigator considered ARIA-H to be due to a head injury.

[b] Rash MQG includes the following preferred terms which occurred higher on study drug than placebo: acne, erythema, infusion site rash, injection site rash, rash, rash erythematous, rash pruritic, skin reactions, and urticaria.

Abbreviations: LEC10-BW, lecanemab 10 mg/kg biweekly; MQG, medical query group

Grouping of terms may be performed to detect a signal that would not otherwise be seen if similar terms were evaluated individually. In addition to the grouped terms noted as a medical query group (MQG) in the table above, these included infection (30% on lecanemab vs 26% on placebo, driven by upper respiratory tract infection in 3% for lecanemab vs 2% for placebo), arrhythmia (5% on lecanemab vs 4% for placebo, driven by atrial fibrillation and atrial flutter in 3% for lecanemab vs 2% for placebo; an imbalance was also observed in 201 Core), and hemorrhage (driven by hematuria that occurred in 2% for lecanemab vs 1% for placebo).

TEAEs occurred in 74% (1020/1385) of subjects in 301 OLE. Dr. Erten-Lyons notes that the most common (≥5%) TEAEs in 301 OLE were infusion-related reactions (13%), COVID-19 (13%), ARIA-H microhemorrhages (12%), ARIA-E (8%), headache (6%), and fall (6%). Similar to the findings in the original review of 201 Core, the incidence of falls in 301 Core was not greater in lecanemab (10.5%) than in placebo (9.7%), and the incidence of falls in the 301 Core and OLE combined is within the reported rate of 29% for adults at least 65 years old in the general population reporting at least 1 fall in the previous year. [7]

Laboratory Findings

Dr. Erten-Lyons notes that the primary laboratory finding in 201 Core was a transient decrease in lymphocytes and an increase in neutrophils after the first infusion of lecanemab, as noted in Section 5.2 of the approved label. She notes that in 301 Core, blood collection

[7] Bergen G, Stevens MR, Burns ER. Falls and Fall Injuries Among Adults Aged ≥65 Years — United States, 2014. MMWR Morb Mortal Wkly Rep 2016;65:993–998. DOI: http://dx.doi.org/10.15585/mmwr.mm6537a2external icon

only occurred prior to the infusion; therefore, any changes in lymphocytes and neutrophils immediately after an infusion could not be assessed.

Dr. Erten-Lyons finds no clear trends or differences in hematology, chemistry, liver chemistry, or urinalysis between placebo and lecanemab in 301 Core. She also does not find an excess of laboratory-related TEAEs for lecanemab compared to placebo other than hematuria; similar to observations in 201 Core, hematuria occurred in 2% on lecanemab vs 1% on placebo, for which she notes insufficient data to determine whether hematuria is related to lecanemab administration, and for which urinalysis did not suggest a lecanemab-related increased in red blood cells.

Vital Signs

There were no clinically significant changes in vital sign parameters in subjects treated with lecanemab. Dr. Erten-Lyons did not identify trends in mean values for vital signs that were different between lecanemab and placebo in 301 Core. She finds shift from baseline of pulse rate > 100, respiratory rate < 12, respiratory rate > 20, and weight decrease at least 7% from baseline that occurred with a difference of approximately 3% more frequently for lecanemab than in placebo. As Dr. Erten-Lyons notes, the significance of these findings is not clear. She did not identify an imbalance of at least 2% in TEAEs related to vital signs in 301 Core.

ECG/QT

There were no clinically meaningful changes in ECG parameters in subjects treated with lecanemab. There were 6 TEAEs of QT prolongation on lecanemab vs none on placebo in 301 Core; this finding was not supported by prolongations of QT interval on ECGs overall. In accordance with ICH E14 guidelines for monoclonal antibodies, a thorough QT study was not conducted.

Subgroup Analyses

In 301 Core, there were some differences (approximately 2 to 5%) in incidence of infusion-related reactions, ARIA-E, ARIA-H, superficial siderosis, and headache TEAEs between males and females, for both lecanemab and placebo, of unclear significance. Dr. Erten-Lyons notes that the incidence of ARIA-E was lowest in subjects who were at least 80 years old. She considers that the inflammatory response against amyloid may not be as robust in patients greater than 80 years old. However, age-related findings are limited by the relatively small number of subjects in age groups of less than 65 years (N=175 for lecanemab) and 80 years or older (N=130 for lecanemab) compared with subjects at least 65 to less than 80 years old (N=593 for lecanemab). The numbers of subjects of race other than White and subjects in regions other than North America were too few to make any meaningful comparisons by race or by region. She does not identify a pattern of increased risk when comparing subjects with mild cognitive impairment or mild Alzheimer's disease.

Other Events of Interest

Amyloid-Relating Imaging Abnormalities (ARIA)

Monoclonal antibodies directed against aggregated forms of beta amyloid, including lecanemab, can cause amyloid related imaging abnormalities (ARIA) characterized as ARIA with edema (ARIA-E), which can be observed on MRI as brain edema or sulcal effusions, and ARIA with hemosiderin deposition (ARIA-H), which includes microhemorrhage and superficial siderosis. ARIA-E or ARIA-H may occur in isolation or concurrently. ARIA-H frequently occurs in association with an occurrence of ARIA-E.

Incidence

The following discussion refers to data from 301 Core unless otherwise indicated.

Table 6, extracted from Dr. Erten-Lyon's review, shows the incidence of ARIA events within 30 days of a dose of lecanemab, and the incidence of intracerebral hemorrhage within 40 days of a dose of lecanemab in 301 Core. ARIA-E or ARIA-H may occur in isolation or concurrently. ARIA-H frequently occurs in association with an occurrence of ARIA-E. Current management of ARIA is not based on such relationships.

Table 6 : Incidence of Treatment Emergent ARIA or Cerebral Hemorrhage in 301 Core

	Placebo N=897 n (%)	Lecanemab N=898 n (%)
ARIA	84 (9)	191 (21)
Symptomatic ARIA	2 (0.2)	29 (3)
ARIA-E	15 (2)	113 (13)
ARIA-H Isolated ARIA-H	80 (9) 69 (8)	152 (17) 78 (9)
ARIA-H microhemorrhage	68 (8)	126 (14)
ARIA-H superficial siderosis	21 (2)	50 (6)
Intracerebral Hemorrhage*	0 (0)	6 (0.7)

**Numbers based on PT of cerebral hemorrhage > 1 cm occurring within 40 days after last dose of study drug.*
*Source: Extracted from Clinical Analyst created table. [tariasum1.rtf] [tariasum1.sas] 12APR2023, 09:49**

In 301 Core, ARIA occurred in 21% of subjects on lecanemab and in 9% of subjects on placebo. The increased incidence compared to 201 Core where ARIA occurred in 12% of

subjects on lecanemab and 5% on placebo, is driven by an increase in the incidence of ARIA-H in 301 Core and that occurred in 6% on lecanemab and 5% on placebo in 201 Core. Dr. Erten-Lyons notes that this difference may be due to the larger number and longer follow-up of ApoE ε4 carriers in 301 Core. Most ARIA-E was co-occurring with ARIA-H; the incidence of isolated ARIA-E (i.e., incidence of ARIA-E in subjects who did not have ARIA-H at the same time on any given MRI) was 4% (36/898) on lecanemab and 0.4% (4/897) on placebo. There was little imbalance in isolated ARIA-H between lecanemab in 301 Core, consistent with the observation in 201 Core. Among new lecanemab exposures in 301 OLE (n=714), the incidences of ARIA (20%), ARIA-E (14%), and ARIA-H (15%) were similar to the incidence in 301 Core. In the combined 301 Core and OLE group (n=1612), the incidence of ARIA overall (23%), ARIA-E (14%), and ARIA-H (18%) was also similar to that in 301 Core alone.

Cerebral Hemorrhage

Dr. Erten-Lyons finds that intracerebral hemorrhage greater than 1 cm occurring within 40 days after the last dose of study drug, was reported in 0.7% (6/898) of subjects on lecanemab and in 0.1% (1/897) subject on placebo in 301 Core (excluding a subject on placebo identified as having intracranial hemorrhage/temporal lobe hemorrhage with no size indicated). Four of the 6 subjects on lecanemab had cerebral hemorrhage in the setting of ARIA-E or ARIA-H. Three additional subjects, all with placebo exposure in 301 Core, had cerebral hemorrhage greater than 1 cm occurring within 40 days after the last dose of lecanemab in the OLE. One additional cerebral hemorrhage in 301 OLE in the setting of ARIA-E and ARIA-H and 6 days after a biopsy for glioblastoma is not included because it occurred 91 days after the last dose of lecanemab. The incidence of cerebral hemorrhage > 1 cm occurring within 40 days after the last dose of lecanemab in the lecanemab treated subjects in 301 Core and OLE combined is 0.6% (9 out of 1612). Use of anticoagulants was associated with an increased risk as discussed in a presentation of antithrombotic use, below.

ApoE ε4 Genotype

ApoE ε4 homozygotes have been previously shown to have an increased incidence of ARIA compared to heterozygotes and noncarriers in subjects taking monoclonal antibodies directed against aggregated forms of beta amyloid, including lecanemab. In 301 Core, 16% (141/898) of subjects in the lecanemab group were ApoE ε4 homozygotes, 53% (479/898) were heterozygotes, and 31% (278/898) were noncarriers. In 301 Core, the incidence of ARIA was higher in ApoE ε4 homozygotes than in heterozygotes or in noncarriers as shown in Table 7 below. Similar findings were observed in subjects who were new to lecanemab in 301 OLE.

Table 7: Incidence ARIA by ApoE ε4 Genotype in Subjects Exposed to Lecanemab, Study 301 Core

	Non-Carriers		Heterozygote		Homozygote	
	Placebo n=286 n (%)	Lecanemab N=278 n (%)	Placebo N=478 n (%)	Lecanemab N=479 n (%)	Placebo N=133 n (%)	Lecanemab N=141 n (%)
ARIA	11 (4)	37* (13)	44 (9)	91* (19)	29 (22)	63 (45)
ARIA-E	1 (0.3)	15 (5)	9 (2)	52 (11)	5 (4)	46 (33)
ARIA-H	11 (4)	32 (12)	41 (9)	66 (14)	28 (21)	54 (38)
Cerebral Hemorrhage	0	1 (0.4)	0	3 (0.6)	0	2 (1)

Source: Clinical Analyst Created. Safety population and TRTEMFL = Y;[taeariaapoe1.rtf] [taeariaapoe1.sas] 12APR2023, 12:2
** Includes cerebral hemorrhage within 40 days after last dose of study drug (subject 23061043 with cerebral hemorrhage 40 days after last dose on lecanemab included, and excludes (b) (6) with cerebral hemorrhage > 90 days after last dose on placebo).*

Dr. Erten-Lyons shows that among subjects treated with lecanemab, symptomatic ARIA-E occurred in 9% of ApoE ε4 homozygotes, 2% of heterozygotes, and 1% of noncarriers. Serious events of ARIA occurred in 3% of ApoE ε4 homozygotes, and approximately 1% of heterozygotes and noncarriers. Among subjects treated with lecanemab who had ARIA-E, severe radiographic ARIA-E was greatest in ApoE ε4 homozygotes (15%, 7/46) compared to heterozygotes (4%, 2/51) or noncarriers (0/30). Among subjects treated with lecanemab who had ARIA-H, severe radiographic ARIA=H was greatest in ApoE ε4 homozygotes (35%, 19/54) compared to heterozygotes (14%, 9/66) or noncarriers (9%, 3/32).

Among the 9 subjects with treatment emergent intracerebral hemorrhage on lecanemab in 301 Core and OLE, 3 were homozygous for ApoE ε4, 4 were ApoE ε3/ε4, and 2 were ApoE ε3/ε3. Dr. Erten-Lyons notes that APOE ε4 and ε2 alleles have been associated with increased risk of intracerebral hemorrhage[8]. In 301 Core, the incidence of intracerebral hemorrhage was 0/611 in ε4 carriers on placebo (excluding 1 subject with cerebral hemorrhage more than 90 days after the last dose of placebo) versus 5/620 in ε4 carriers on lecanemab. As Dr. Erten-Lyons notes, interpretation of these data with respect to the risk of cerebral hemorrhage in ApoE ε4 carriers on lecanemab is limited because out of the 5 ε4 carriers with intracerebral hemorrhage, 2 homozygotes were on the antiplatelet medication ticagrelor or the anticoagulant warfarin with aspirin, and one heterozygote subject was on the anticoagulant rivaroxaban prior to intracerebral hemorrhage. The limited data do not allow for a conclusion about the risk of intracerebral hemorrhage in ApoE ε4 carriers on lecanemab.

[8] Marini et al. Association of Apolipoprotein E With Intracerebral Hemorrhage Risk by Race/Ethnicity. JAMA Neurol. 2019;76(4):480-491. doi:10.1001/jamaneurol.2018.4519

Because of the increased incidence of ARIA, including symptomatic, serious, and severe radiographic ARIA in ApoE ε4 homozygotes, labeling will state that testing for ApoE ε4 status should be performed prior to initiation of treatment with lecanemab to inform the risk of developing ARIA.

Symptoms

The majority of ARIA cases in 301 Core were asymptomatic, similar to the findings in 201 Core in the original BLA as described in the currently approved label. The incidence of symptomatic ARIA was 3.2% (29/898) in subjects treated with lecanemab compared to 0.2% (2/897) in the placebo group in 301 Core. Of those, 2.8 % (25/898) of subjects treated with lecanemab had symptomatic ARIA-E, 1% (9/898) had symptomatic ARIA-H microhemorrhage, and 0.2% (2/898) had symptomatic superficial siderosis. Of the 29 lecanemab treated subjects with symptomatic ARIA, 45% (13/29) were ApoE ε4 homozygotes, 41% (12/29) were heterozygotes, and 14% (4/29) were noncarriers.

The most common symptom in subjects with ARIA-E on lecanemab was headache (12/898, 1.3% overall; 12/25, 48% of subjects with ARIA-E); other reported symptoms included confusion, dizziness, nausea, visual changes, and focal neurologic deficits, consistent with symptoms reported for this class of drugs.

Severity of clinical symptoms in ARIA-E was mild in 12 subjects, moderate in 11 subjects, and severe in 2 subjects on lecanemab. The incidence of serious symptomatic ARIA was 0.7% (6/898) in subjects treated with lecanemab; 6 subjects had serious symptomatic ARIA-E, with one also having co-occurring serious symptomatic ARIA-H. Among the subjects with serious symptomatic ARIA, 2 were homozygotes, 2 were heterozygotes, and 2 were noncarriers.

Clinical symptoms resolved in approximately 79% (23/29) of subjects with ARIA overall (including 1 with sequela), in 92% (23/25) of subjects with symptomatic ARIA-E, and resolved or were resolving in 73% (8/11) of subjects with symptomatic ARIA-H, within the period of observation.

The incidence of symptomatic ARIA and of serious symptomatic ARIA in 301 OLE was similar to that observed in 301 Core.

Dr. Erten-Lyons notes that two subjects with symptomatic ARIA-E, both ApoE ε4 homozygotes, complained of headache (mild to moderate in clinical severity) and were dosed through the headache with subsequent MRI showing severe ARIA-E, in addition to Subjects (b) (6) and (b) (6) who were dosed through their headaches and died subsequently of cerebral hemorrhage and ARIA-E, respectively. She suggests that clinicians should have a low threshold to obtain imaging, even in the setting of mild headaches, in ApoE ε4 carriers who are at higher risk of having severe ARIA-E. This is consistent with the currently approved labeling that recommends that if a patient experiences symptoms suggestive of ARIA, clinical evaluation should be performed, including MRI if indicated.

Seizures, including status epilepticus, have been associated with ARIA after administration of monoclonal antibodies directed against aggregated forms of beta amyloid as noted in the approved label for lecanemab. In addition, patients with Alzheimer's disease may be at increased risk for seizures.[9] In 301 Core, seizures occurring in the setting of ARIA or cerebral hemorrhage occurred in 0.2% (3/898) subjects on lecanemab and 0.1% (1/897) subjects on placebo. Seven subjects in the OLE (7/1385, 0.5%) had an ARIA related seizure. Seizures, including those related to ARIA-E and ARIA-H, will be discussed later in this document.

Radiographic Severity

Among the 898 subjects treated with lecanemab in 301 Core, the maximum radiographic severity for ARIA-E was mild in 4%, moderate in 7%, and severe in 1%. The maximum radiographic severity for ARIA-H microhemorrhage was mild in 9%, moderate in 2%, and severe in 3%. The maximum radiographic severity for superficial siderosis was mild in 4%, moderate in 0.9%, and severe in 0.4%. The findings in 301Core/OLE combined are consistent with those in 301 Core alone. The findings are generally consistent with those observed in 201 Core; differences are likely due to increased exposure with a larger clinical trial database in 301 Core.

Timing of ARIA Events

Routine Safety MRIs to monitor for ARIA were to be performed to prior to the 5th, 7th, 14th, and 27th, doses and 90 days post the last dose in 301 Core. For subjects continuing into the OLE, the MRI performed prior to the 40th dose was considered as the OLE baseline.
Table 8, extracted from Dr. Erten-Lyons' review, shows the timing of first ARIA-E events in the lecanemab group in 301 Core.

[9] Pandis D, Scarmeas N. Seizures in Alzheimer Disease: Clinical and Epidemiological Data: Seizures in Alzheimer Disease. Epilepsy Currents. 2012; 12: 184-187.

Table 8 Timing of first ARIA-E events in Lecanemab-treated Subjects in 301 Core

Number of Doses Prior to ARIA-E	Number of subjects experiencing a first ARIA-E	Cumulative frequency of first ARIA-E N (%)
1	1	1 (1)
2	1	2 (2)
3	7	9 (8)
4	44	53 (47)
5	4	57 (50)
6	24	81 (72)
11	2	83 (73)
12	6	89 (79)
13	15	104 (92)
21	1	105 (93)
22	1	106 (94)
23	1	107 (95)
24	3	110 (97)
25	1	111 (98)
26	1	112 (99)
39	1	113 (100)

Dr. Erten-Lyons finds that in 301 Core, as in 201 Core, the majority of ARIA-E radiographic events (approximately 72%) occurred prior to the 7th dose. Ninety-two percent occurred prior to the 14th dose. Dr. Erten-Lyons shows that in 301 Core, additional ARIA-E events continued to occur up to the 39th dose, and in 301 OLE she has identified one subject who had ARIA-E after the 41st dose administered in the Core and OLE. Of subjects with ARIA-E, approximately 8% of had a first episode of ARIA-E prior to the 4th dose. Similarly, in the 301 OLE, among the 98 subjects who had ARIA-E after starting lecanemab in the OLE, 70% of cases had occurred prior to 7th dose and 99% prior to the 12th dose.

She also notes ARIA-H events occurring beyond 30 days after a dose of study drug occurred more frequently in lecanemab-treated subjects (5%, 44/898) than on placebo (0.6%, 5/897) in 301 Core. The mean time for late occurring ARIA-H after a dose of lecanemab was approximately 96 days (32-359 days) vs 75 days (34 to 129 days) for placebo. The late occurring ARIA-H events on lecanemab occurred primarily in ApoE ε4 carriers (28/44 subjects with late occurring events). Approximately 50% of the late occurring ARIA-H microhemorrhages were radiographically severe (with over 10 ARIA-H microhemorrhages) while none were severe on placebo. Late occurring ARIA-H was similarly observed in the 301 OLE. The relationship of late occurring ARIA-H to study drug is unknown; ARIA-H can occur in the absence of lecanemab, with ApoE ε4 carriers at greatest risk.

In 301 Core, a first event of ARIA-E in subjects on lecanemab resolved by the 12th week after detection in 52% (59/113) of subjects, by 17 weeks in 81% (91/113) of subjects, and in all subjects by the end of the study, resolving on average in 92 days (16-374 days). Time to resolution in 301 OLE was similar to that observed in 301 Core.

In 301 Core, approximately 25% (28/113) of subjects with ARIA-E on lecanemab had more than 1 treatment-emergent event of ARIA E. Four of those subjects had more than 2 events. Although there is experience in subjects having more than 1 episode of ARIA, the data are too limited to make generalizable recommendations regarding implications or outcomes of recurrent ARIA. The clinical studies required interruption of dosing for symptomatic ARIA-E or ARIA-H. Thus, there is no experience in Study 301 Core or OLE or in 201 OLE with continued dosing through symptomatic, radiographically mild ARIA-E that is allowed for in the approved label and that is the current class approach to dosing.

Antithrombotic Use

Dr. Erten-Lyons notes that in Study 301, anticoagulation was allowed if optimized and stable for at least 4 weeks before screening. If treatment with thrombolytic drugs was required, study drug was temporarily suspended until stabilization or resolution of the medical condition requiring thrombolytic therapy. The protocol also excluded patients with a bleeding disorder not under adequate control (including a platelet count less than 50,000 or an international normalized ratio greater than 1.5 if not on anticoagulation treatment), more than 4 microhemorrhages (defined as 10 mm or less at the greatest diameter), a single macrohemorrhage greater than 10 mm at greatest diameter, an area of superficial siderosis, aneurysms, and vascular malformations. Of note, whereas Study 201 excluded patients with uncontrolled hypertension with a history of blood pressure consistently above 165/100 mm Hg at screening, that was not an exclusion criterion in Study 301.

In 301 Core, consistent with the findings in 201 Core described in the label, subjects who received lecanemab and an antithrombotic medication (aspirin, other antiplatelet, or anticoagulant) did not have an increased risk of ARIA-H compared to subjects who did not receive an antithrombotic medication preceding ARIA-H. In subjects treated with lecanemab in 301 Core, subjects who received antithrombotic medication preceding an intracerebral hemorrhage event had a slightly higher incidence of cerebral hemorrhage (0.9%, 3/328; these were the antiplatelet drug ticagrelor and the anticoagulants warfarin with aspirin and rivaroxaban), particularly those on an anticoagulant (alone or combined with antiplatelet or aspirin, 2.5%, 2/79), than those who did not receive an antithrombotic (0.6%, 3/545), as shown in **Table 9** below.

Table 9: Antithrombotic Use and Risk of Cerebral Hemorrhage

	Cerebral Hemorrhage	
	Placebo	**Lecanemab**
Not on antithrombotic	0/584	3/545 (0.6)
On antithrombotic	0/304	3/328 (0.9)
Aspirin ≤81 mg	0/144	0/162
Aspirin ≥81 mg, other antiplatelet or dual antiplatelet	0/107	1/116 (0.9)
Anticoagulation	0/72	2/79 (2.5)

Source: Extracted from Eisai Table sBLA IR9-1mod, submitted May 1, 2023, cerebral hemorrhage>1cm occurring within 40 days of last dose included

Among the subjects with intracerebral hemorrhage on lecanemab, as shown in **Table 10** below, 2 were ApoE ε4 homozygotes (1 of whom was on ticagrelor and had ongoing ARIA-E; 1 of whom was on warfarin), 3 were ApoE ε4 heterozygotes (1 of whom was on the anticoagulant rivaroxaban, had 3 microhemorrhages at screening, and had ongoing ARIA-E and ARIA-H) and 1 was a noncarrier.

Table 10: Intracerebral Hemorrhage and ApoE ε4 Status in 301 Core

	Lecanemab N=898		
	Noncarrier N=278	Heterozygote N=479	Homozygote N=141
Cerebral Hemorrhage>1cm	1(0.4)	3 (0.6)	2 (1.4)

The small number of events limits definitive conclusions. The limited number of intracerebral hemorrhage events on subjects taking placebo preclude a comparison with the risk of antithrombotic use in placebo. A similarly increased risk of intracerebral hemorrhage in subjects on antithrombotics, particularly anticoagulants, compared to those not on antithrombotics was also observed in combined 301 Core and OLE.

The majority of exposures to antithrombotic medications in 301 Core were to aspirin (76%, 490/646). However, because intracerebral hemorrhages greater than 1 cm in diameter have been observed in subjects taking lecanemab, current labeling recommends that additional

caution should be exercised when considering the administration of antithrombotics or a thrombolytic agent (e.g., tissue plasminogen activator) to a patient already being treated with lecanemab.

Approach to the Management of ARIA

Because risk factors for and clinical presentation of ARIA appear to be similar across anti-amyloid monoclonal antibody products, a standardized approach to management of ARIA for different anti-amyloid monoclonal antibody products is reasonable. As there may be differences between products in incidence and timing of ARIA, MRI monitoring schedule will remain specific for each anti-amyloid monoclonal antibody product. These are the approaches used in the currently approved labeling.

Recommendations for dosing interruptions for ARIA events are shown in Table 11 and Table 12.

Table 11: Dosing Recommendations for Subjects with ARIA-E

Clinical Symptom Severity[1]	**ARIA-E Severity on MRI**		
	Mild	**Moderate**	**Severe**
Asymptomatic	May continue dosing	Suspend dosing[2]	Suspend dosing[2]
Mild	May continue dosing based on clinical judgment	Suspend dosing[2]	
Moderate or Severe	Suspend dosing[2]		

[1] Mild: discomfort noticed, but no disruption of normal daily activity.
Moderate: discomfort sufficient to reduce or affect normal daily activity.
Severe: incapacitating, with inability to work or to perform normal daily activity.

[2] Suspend until MRI demonstrates radiographic resolution and symptoms, if present, resolve; consider a follow-up MRI to assess for resolution 2 to 4 months after initial identification. Resumption of dosing should be guided by clinical judgment.

Table 12: Dosing Recommendations for Subjects with ARIA-H

Clinical Symptom Severity	ARIA-H Severity on MRI		
	Mild	**Moderate**	**Severe**
Asymptomatic	May continue dosing	Suspend dosing[1]	Suspend dosing[2]
Symptomatic	Suspend dosing[1]	Suspend dosing[1]	

[1] Suspend until MRI demonstrates radiographic stabilization and symptoms, if present, resolve; resumption of dosing should be guided by clinical judgment.

[2] Suspend until MRI demonstrates radiographic stabilization and symptoms, if present, resolve; use clinical judgment in considering whether to continue treatment or permanently discontinue lecanemab.

The labeling will recommend a recent MRI prior to initiating treatment and, as Dr. Erten-Lyons notes, prior to the 5th, 7th, and 14th infusions. Labeling also recommends that clinical evaluation should be performed, including MRI, if a patient experiences symptoms suggestive of ARIA. This approach continues to be reasonable, supported by the data in the present submission.

Currently approved labeling recommends that in patients who develop intracerebral hemorrhage greater than 1 cm in diameter during treatment with lecanemab, dosing with lecanemab be suspended until an MRI demonstrates radiographic stabilization and symptoms, if present, resolve, and that prescribers should use clinical judgement in considering whether to continue treatment after radiographic stabilization and resolution of symptoms or permanently discontinue lecanemab. The rationale for this recommendation is that intracerebral hemorrhages can occur in an older population and may have an etiology that is unrelated to cerebral amyloid angiopathy or treatment with an anti-amyloid monoclonal antibody, such as a hypertensive hemorrhage or trauma. Clinicians should consider the potential etiology of the hemorrhage and also the individual risk factors for a patient when deciding whether to continue or permanently discontinue treatment. This recommendation continues to remain appropriate.

Seizures

In Study 301 Core the incidence of having a seizure was 0.7% (6/898) of subjects on lecanemab and 0.4% (4/897). One subject who had a cerebral hemorrhage and seizure 40 days after last dose of lecanemab, in the setting of worsening ARIA-E and ARIA-H was included in these numbers. In 301 Core, seizures occurring in the setting of ARIA or cerebral hemorrhage occurred in 0.2% (3/898) subjects on lecanemab and 0.1% (1/897) subjects on placebo. Seven subjects in the OLE (7/1385, 0.5%) had a seizure in the setting of ARIA or cerebral hemorrhage and 6 subjects (6/1385, 0.4%) had a seizure that was not associated

with ARIA or cerebral hemorrhage. Two of the subjects with seizures (1 in 301 Core and 1 in 301 OLE, included above) had seizures in the setting of cerebral hemorrhage.

Infusion Reactions and Hypersensitivity Reactions

In 301 Core 26% (236/898) of lecanemab subjects vs 7% (64/897) of placebo subjects had at least 1 infusion-related reaction (excluding 2 placebo and 1 lecanemab infusion site reactions). These findings are similar to those observed in 201 Core as described in the label and in 301 OLE and OLE combined. The maximum clinical severity of infusion-related reactions on lecanemab was mild in 69%, moderate in 28%, and severe in 3%. Eleven subjects (1%) in 301 Core had an infusion reaction categorized as a SAE after administration of lecanemab. The infusion reaction occurred at the time of the first infusion in 76% (179/236) subjects who had infusion reactions on lecanemab. Infusions were interrupted because of an infusion-related reaction in 1.4% (13/898) subjects on lecanemab vs 0.7% (6/897) on placebo. Twelve of 898 subjects (1.3%) on lecanemab vs 1/897 (0.1%) in the placebo group had study drug discontinued due to an infusion-related reaction.

Dr. Erten-Lyons notes that 94% (221/236) of subjects who had an infusion-related reaction on lecanemab in 301 Core received subsequent infusions. Forty-four percent (97/221) who had an infusion reaction received at least one preventative medications with subsequent infusions; the most frequently administered were corticosteroids, antihistamines, and analgesics/antipyretics. The incidence of subsequent infusion-related reactions after a first event on lecanemab was similar with (37%, 36/97) and without (35%, 43/124) preventative medication.

Symptoms associated with infusion reactions in Study 301 included increased blood pressure (including subject (b) (6) with blood pressure of 180/85 mm Hg approximately 4 hours after an infusion and (b) (6) with blood pressure of 190/90 mm Hg 2 hours after the first infusion), increased heart rate and respiratory rate, rigors, chills, fevers, cyanosis, headache, syncope, nausea, and vomiting, similar to those described in Core 201 that included fever and flu-like symptoms (chills, generalized aches, feeling shaky, and joint pain). Some subjects experienced hypotension, hypertension, nausea, vomiting, or desaturation.

One subject ((b) (6) had an anaphylactic reaction that included dyspnea, nausea and vomiting, and was treated with epinephrine and solumedrol. In 301 Core, a Hypersensitivity Standardized MedDRA Query grouping (MQG), excluding infusion reactions, occurred in 80/898 (9%) subjects in the lecanemab group vs 65/897 (7%) in the placebo group and were primarily rash-related terms. The Rash MQG grouping was reported in approximately 6% (52/898) in lecanemab and 4% (37/897) in placebo. Rash-related events were mild or moderate. Hypersensitivity also included 1 subject each on lecanemab with lip swelling, periorbital swelling, periorbital edema, urticarial vasculitis, and bronchospasm (and 1 subject each on placebo had periorbital edema and bronchospasm).

In Study 201 Core, after the first infusion, 38% of subjects treated with lecanemab had transient decreased lymphocyte counts and transient increased neutrophil counts. In 301 Core, those measurements were not evaluated post-infusion.

Suicidal behavior/ideation

There is not a signal for suicide-related events in Study 301 Core or OLE.

Abuse Potential

Dr. Erten-Lyons did not identify a signal for drug abuse potential, withdrawal or rebound.

Immunogenicity

As noted in the original review, the ADA assay used by the applicant was not reliable for accurate classification of ADA status, due to interference by serum lecanemab concentrations, possibly resulting in an underestimation of the incidence of antibody formation. As a result, no comparisons could be conclusively made in the incidence of TEAEs in ADA negative vs positive subjects. Postmarketing requirements (4384-2 and 4384-3) were imposed with the January 6, 2023, accelerated approval, to improve the assay sensitivity and to use the improved and validated assay to assess the impact of antibody formation on pharmacokinetics, pharmacodynamics, safety, and efficacy of lecanemab in subjects enrolled in the confirmatory study. (b) (4), (b) (5) The impact of immunogenicity on pharmacokinetics, pharmacodynamics, efficacy and safety will be evaluated when data to support the postmarketing requirements (PMRs) are submitted.

Carcinogenicity

Dr. Erten-Lyons identified an imbalance in the incidence of neoplasms between lecanemab (8.6%, 77/898) and placebo (6.5%, 58/897). There were no individual neoplasms in which the rate for lecanemab was more than 0.6% greater than in placebo. The mean duration of exposure of approximately 17 months (range of 0.5 to 42 months) in 301 Core and OLE overall may not be sufficient to fully characterize the carcinogenic potential in humans.

Human Reproduction and Pregnancy

There are no data on the use of lecanemab in pregnant women.

Safety Summary

There are no safety issues that would preclude full approval of lecanemab for the proposed indication.

ARIA is characterized by radiographic findings on MRI and by symptoms associated with ARIA. Recommendations for clinical evaluation, including MRI monitoring and symptom recognition, are provided for in the prescribing information (sections 2.3, 2.4, and 5.1) and in the medication guide.

We continue to agree that a Risk Evaluation and Mitigation Strategy (REMS) is not necessary to ensure the benefits of lecanemab outweigh its risks. The prescribing population will likely consist of memory disorder specialists who are familiar with Alzheimer's disease. Labeling will be used to communicate the risk of ARIA.

The risk of ARIA, particularly in patients who are ApoE ε4 homozygotes, and the risk of intracerebral hemorrhage, warrant a boxed warning. Testing for ApoE ε4 status should be performed prior to initiation of treatment with lecanemab to inform the risk of developing ARIA. Labeling will convey the risk of ARIA and intracerebral hemorrhage and include recommendations for MRI monitoring, radiographic classification criteria for ARIA severity, the need for assessment of symptoms associated with ARIA throughout treatment, and considerations for continuing lecanemab in the setting of ARIA. A Medication Guide will communicate the risks to patients and caregivers. Enhanced pharmacovigilance for ARIA, requested with the accelerated approval, will continue to be requested. If new safety information becomes available, the need for a REMS can be reevaluated.

The Applicant provided a summary of their educational plan for providers regarding identification of patients appropriate for lecanemab treatment, MRI safety monitoring and MRI diagnosis and management of ARIA, and identification and management of infusion-related reactions. The Applicant also plans an educational program for patients and caregivers. They will provide live access to medical information specialists on weekdays. The (b) (4) The Applicant has launched an "unbranded" website providing educational materials at www.UnderstandingARIA.com.

8. Advisory Committee

An advisory committee meeting was held on June 9, 2023, to discuss the data from Study 301 and whether the data verify the clinical benefit of lecanemab for the treatment of AD, and to discuss whether the data impact the established benefit-risk assessment for lecanemab.

The committee discussed whether the data from Study 301 showed clear and robust evidence of effectiveness. The committee voted unanimously, 6-0, that the data confirm the clinical benefit of lecanemab for the treatment of AD.

The committee then discussed the overall benefit-risk assessment of lecanemab for the treatment of AD. The committee opined that the overall benefit-risk assessment for the population of patients with AD who were enrolled in Study 301 appeared favorable and supported traditional approval.

The panel discussion then focused on the following specific patient subgroups that the Agency had identified in the briefing document and discussion question as being more challenging in assessing benefit-risk.

- Apolipoprotein E (ApoE) ε4 homozygotes
- Patients requiring concomitant treatment with anticoagulant agents
- Patients with cerebral amyloid angiopathy

Apolipoprotein E (ApoE) ε4 homozygotes
The presence of the ApoE E ε4 allele increases the risk of ARIA, with greater risk observed in homozygotes than heterozygotes. In Study 301, subgroup analyses by ApoE ε4 status by carrier or noncarrier demonstrated a statistically significant treatment effect in both groups; however, a further subgroup analysis of the carriers by heterozygote and homozygote status suggests that there could potentially be lower efficacy in the homozygote subgroup treated with lecanemab; however, there are limitations to the interpretability of this data such as the small size of this subgroup.

The committee indicated that they thought that the drug was still effective in ApoE ε4 homozygotes, noting the consistency across the secondary endpoints and limitations with a small sample size. The consensus appeared to be that the benefit-risk remained favorable for ApoE ε4 homozygotes, although some members questioned if the dosing regimen could be further optimized in this population. The committee also noted that language regarding recommendations for ApoE genotyping to inform risk should be stronger in labeling.

Patients requiring concomitant treatment with anticoagulant agents
In Study 301, baseline use of antithrombotic medication (aspirin, other antiplatelets, or anticoagulants) was allowed if the patient was on a stable dose. The majority of exposures to antithrombotic medications were to aspirin. Antithrombotic medications did not increase the risk of ARIA with lecanemab. Patients taking lecanemab who received an antithrombotic medication preceding an intracerebral hemorrhage event had a slightly higher incidence of intracerebral hemorrhage (0.9%, 3/328 patients) than those who did not receive an antithrombotic (0.6%, 3/545 patients). Patients taking lecanemab with an anticoagulant alone or combined with an antiplatelet medication or aspirin had an incidence of intracerebral hemorrhage of 2.5% (2/79 patients).

Current labeling advises: “Because intracerebral hemorrhages greater than 1 cm in diameter have been observed in patients taking LEQEMBI, additional caution should be exercised when considering the administration of anticoagulants or a thrombolytic agent (e.g., tissue plasminogen activator) to a patient already being treated with LEQEMBI.”

There were split opinions in the panel regarding whether patients should be treated with concomitant anticoagulant medications and lecanemab. However, more panelists favored not excluding patients taking anticoagulant medication from treatment with lecanemab and allowing for prescriber clinical judgement based on individual evaluation.

Patients with cerebral amyloid angiopathy
Risk of ARIA may be greater in patients with underlying cerebral amyloid angiopathy (CAA) or more severe CAA. In the clinical trials with lecanemab, patients with MRI findings consistent with CAA (i.e., more than 4 microhemorrhages, a single hemorrhage greater than 10mm, an area of superficial siderosis) were not enrolled; however, there is a high background rate of CAA in AD and many individuals with CAA do not have the characteristic findings on MRI. This makes identification of patients with CAA difficult and limits the ability to make specific recommendations to mitigate any increased risk of ARIA, if CAA does pose an increased risk. There are individuals with identified CAA pathology who have had serious outcomes during treatment with lecanemab; however, given the high background rate of CAA, there are also many individuals who likely have CAA pathology who have received treatment with lecanemab and have not experienced significant adverse events. The current prescribing information does not specifically address the potential risk of lecanemab use with CAA but does list risk factors for intracerebral hemorrhage such as prior cerebral hemorrhage greater than 1 cm in greatest diameter, more than 4 microhemorrhages, superficial siderosis, evidence of vasogenic edema. The prescribing information states that caution should be exercised when considering the use of lecanemab in patients with these risk factors.

During the discussion, FDA provided information on the criteria for contraindications, noting that contraindications were typically informed by clinical data, and, in this situation, there is a theoretical risk but little data in patients that were excluded to adequately define the risk. The panel noted that it would be difficult to exclude patients for a condition that does not have definitive clinical diagnostic criteria. However, it was noted that the potential risk with CAA could be more clearly stated in the label which could then help inform prescribers and patients about potential risks.

9. Pediatrics

Pediatric patients were not enrolled in trials because AD typically affects older adults. The applicant was granted a waiver for Pediatric Research Equity Act (PREA) requirements for this reason.

10. Other Relevant Regulatory Issues

- Dr. Krudys did not identify any Good Clinical Practice (GCP) issues.
- Dr. Krudys concludes that the Applicant has adequately disclosed financial interests/arrangements with clinical investigators.
- The Office of Scientific Investigations (OSI) conducted inspections of three clinical sites. Site selection was based on risk ranking in the clinical investigator site selection tool, enrollment, and history of prior inspections. The review concludes that Study 301 appears to have been conducted adequately and the data generated by the sites inspected appear acceptable in support of the respective indication.

11. Labeling

Labeling negotiations with the Applicant have been completed and the Applicant has accepted all recommended changes.

12. Postmarketing Recommendations

Risk Evaluation and Management Strategies (REMS)

The Agency has determined that at this time there is not a need for a REMS. Please refer to the review by Dr. Darling (December 16, 2022) from the Division of Risk Management for further details of this assessment.

Postmarketing Requirements (PMRs) and Commitments (PMCs)

PMRs will be as follows:

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

treatments). When available, the study should provide a comparison of safety outcomes to estimated background rates in an appropriate comparator population.

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

- Further characterize the safety of treatment with lecanemab in patients who are homozygous for ApoE ε4. We would accept information on this risk from a randomized, clinical trial in participants with early preclinical Alzheimer's disease and intermediate amyloid (i.e., AHEAD 3-45 Study). Ensure that approximately 15% of the population, distributed equally among lecanemab and control, is homozygous for ApoE ε4.

An agreed upon PMC is as follows:

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

13. Comments to the Applicant

The request for enhanced pharmacovigilance, as specified in the initial accelerated approval letter, will remain in effect.

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/

RANJIT B MANI
07/06/2023 11:13:01 AM

SALLY U YASUDA
07/06/2023 11:14:46 AM

EMILY R FREILICH
07/06/2023 01:02:01 PM

TERESA J BURACCHIO
07/06/2023 03:52:44 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761269Orig1s001

CLINICAL REVIEW(S)

CLINICAL REVIEW

Application Type	Efficacy Supplement
Application Number(s)	761269 (S-001)
Priority or Standard	Priority
Submit Date(s)	01/06/2023
Received Date(s)	01/06/2023
PDUFA Goal Date	07/06/2023
Division/Office	Division of Neurology 1/Office of Neuroscience
Reviewer Name(s)	Kevin Krudys, PhD
Review Completion Date	07/04/2023
Established/Proper Name	Lecanemab-irmb
Trade Name	Leqembi
Applicant	Eisai Inc.
Dosage Form(s)	Solution for injection
Applicant Proposed Dosing Regimen(s)	10 mg/kg as an intravenous infusion every two weeks
Applicant Proposed Indication(s)/Population(s)	(b) (4) treatment for Alzheimer's disease
Recommendation on Regulatory Action	Traditional Approval
Recommended Indication(s)/Population(s) (if applicable)	Treatment of Alzheimer's disease

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Glossary

Aβ	amyloid beta
AC	advisory committee
AD	Alzheimer's disease
AE	adverse event
ADA	anti-drug antibody
ADAS-Cog	Alzheimer's Disease Assessment Scale – Cognitive Subscale
ADCOMS	Alzheimer's Disease Composite Score
ANCOVA	analysis of covariance
ApoE	apolipoprotein E
ARIA	amyloid-related imaging abnormalities
ARIA-E	amyloid-related imaging abnormalities-edema
ARIA-H	amyloid-related imaging abnormalities-hemorrhage
BLA	biologics license application
BRF	Benefit Risk Framework
CDER	Center for Drug Evaluation and Research
CDR	Clinical Dementia Rating
CDR-SB	Clinical Dementia Rating Sum of Boxes
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COVID-19	coronavirus disease 2019
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSF	cerebrospinal fluid
CSR	clinical study report
CSS	Controlled Substance Staff
DIAD	dominantly inherited Alzheimer's disease
DMC	data monitoring committee
DSMB	Data Safety Monitoring Board
eCTD	electronic common technical document
EQ-5D-5L	European Quality of Life-5 Dimensions 5 Level version
FAS	full analysis set
FDA	Food and Drug Administration
GCP	good clinical practice
GFAP	glial fibrillary acidic protein
ICH	International Council for Harmonization
IgG1	immunoglobulin G1

IMC	Interim Monitoring Committee
IND	Investigational New Drug Application
ISE	integrated summary of effectiveness
ITT	intent to treat
LS	least square
MCI	mild cognitive impairment
mITT	modified intent to treat
MMRM	mixed-effects model repeated measures
MMSE	Mini-Mental State Examination
MRI	magnetic resonance imaging
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NfL	neurofilament light chain
NIA-AA	National Institute on Aging at the National Institutes of Health and the Alzheimer's Association
NME	new molecular entity
OCS	Office of Computational Science
OLE	open-label extension
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PD	pharmacodynamics
PET	Positron Emission Tomography
PI	prescribing information or package insert
PK	pharmacokinetics
PKPD	pharmacokinetic-pharmacodynamic
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PRO	patient reported outcome
RAR	response adaptive randomization
QoL-AD	Quality of Life in Alzheimer's Disease
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
sBLA	supplemental Biologics License Application
TEAE	treatment emergent adverse event
SUVR	standard uptake value ratio
vMRI	volumetric magnetic resonance imaging
WMS-IV LM II	Wechsler Memory Scale-IV Logical Memory (subscale) II

1. Executive Summary

1.1. Product Introduction

Lecanemab is a humanized immunoglobulin G1 (IgG1) monoclonal antibody targeting aggregated forms of amyloid beta (Aβ). Extracellular deposits of Aβ are one of the two pathological hallmarks of Alzheimer's disease, along with intracellular aggregates of hyperphosphorylated tau in the form of neurofibrillary tangles. Different Aβ species are defined by their size and structure and include monomers, oligomers and protofibrils, and insoluble fibrils and plaques. Accumulation of Aβ in the brain has been proposed to be an important part of the disease process which precedes neurodegeneration and clinical decline. Lecanemab reduces levels of brain Aβ plaque by targeting aggregated forms of Aβ, with highest affinity for large soluble protofibrils.

The applicant's proposed indication is (b) (4) treatment for Alzheimer's disease. The dosing regimen is an intravenous infusion of 10 mg/kg lecanemab over approximately one hour, administered once every two weeks with no titration. Lecanemab is available as a 100 mg/mL solution in a single-dose vial for intravenous infusion.

Lecanemab received accelerated approval on January 6, 2023, with the proprietary name Leqembi. This application contains the results of the confirmatory study to verify the clinical benefit of lecanemab. Lecanemab is not marketed in any other country.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The clinical benefit of lecanemab for the treatment of Alzheimer's disease has been verified based on the demonstration of a statistically significant and clinically relevant reduction in clinical decline as measured by the Clinical Dementia Rating – Sum of Boxes (CDR-SB) in an adequate and well-controlled study. This conclusion is supported by statistically significant reduction in clinical decline of all clinical secondary endpoints. Brain amyloid plaque was significantly reduced and effects on downstream tau pathophysiology and neurodegeneration support the observations on the clinical outcome measures.

Study 301 is also adequate to satisfy postmarketing requirement 4384-1 to verify the clinical benefit of lecanemab

1.3. Benefit-Risk Assessment

Benefit-Risk Integrated Assessment

Lecanemab is a monoclonal antibody directed against aggregated soluble and insoluble forms of amyloid beta. The proposed indication is the treatment of Alzheimer's disease. This reviewer recommends traditional approval based on efficacy data from an adequate and well-controlled study that has verified the clinical benefit of lecanemab.

Alzheimer's disease is an irreversible and progressive disease that affects memory, thinking, and behavior and is ultimately fatal. After a diagnosis of Alzheimer's disease dementia, the average survival is 4 to 8 years. Alzheimer's disease was the sixth leading cause of death in the United States in 2019. Acetylcholinesterase inhibitors and the N-methyl-D-aspartate receptor antagonist memantine are approved therapies, but they do not target the underlying pathology of the disease and their effects are modest and short-lived. Aducanumab and lecanemab were approved under the accelerated approval pathway based on reduction of brain amyloid plaque as measured by positron emission tomography (PET) for the treatment of Alzheimer's disease, specifically patients with mild cognitive impairment (MCI) or mild dementia stage of disease, but their use to date is limited. There remains an urgent and unmet medical need for additional effective treatments for Alzheimer's disease, and a particular unmet need for effective therapies to delay, halt, or reverse the pathophysiological processes that ultimately lead to the clinical deficits of Alzheimer's disease.

The applicant is seeking conversion of the current accelerated approval to a traditional approval based on results from Study 301 (CLARITY-AD), a multicenter, randomized, double-blind, placebo-controlled, parallel-group study in patients with mild cognitive impairment or mild dementia due to Alzheimer's disease. Patients were required to have evidence of brain Aβ pathology by either visual read of a PET scan or cerebrospinal fluid (CSF) assessment of t-tau/$A\beta_{1-42}$. The study included a 60-day screening period, an 18-month (78-week) placebo-controlled period, and a safety follow-up period of 3 months after the final dose. Patients were randomized to placebo or 10 mg/kg biweekly lecanemab in a 1:1 ratio in the placebo-controlled period. The primary clinical endpoint was the change from baseline in Clinical Dementia Rating Scale- Sum of Boxes (CDR-SB) at Week 79. Secondary endpoints included the change from baseline in brain amyloid plaque levels as measured by PET, and change from baseline in Alzheimer's Disease Assessment Scale – Cognitive Subscale (ADAS-Cog 14), Alzheimer's Disease Composite Score (ADCOMS), and Alzheimer's Disease Cooperative Study – Activities of Daily Living – Mild Cognitive Impairment (ADCS-ADL-MCI) at 18 months.

The primary efficacy endpoint analysis, change from baseline in CDR-SB at Week 79, demonstrated a statistically significant treatment effect in the lecanemab treatment arm compared to placebo (-0.45[-27%], p=0.00005). Nominal statistical significance was reached by Week 27 and maintained through Week 79. Results were robust across sensitivity analyses. Statistically significant results favoring lecanemab were observed

for all 3 multiplicity-controlled secondary clinical endpoints. Lecanemab resulted in a reduction in change from baseline as measured on the ADAS-Cog 14 (-1.442[-26%], p=0.00065), ADCS-ADL-MCI (2.016[-37%], p<0.00001), and ADCOMS (-0.050[-24%], p=0.00002) as compared to placebo. Amyloid PET was assessed in 40% of the overall population (353 patients in the placebo arm and 363 patients in the lecanemab treatment arm). Lecanemab treatment demonstrated a statistically significant treatment effect on change from baseline in brain amyloid as measured by PET and reported as Centiloids at Week 79 (-59.1, p<0.00001).

It is useful to interpret treatment difference as a percent reduction rather than the absolute point difference which depends on the length of the study and the disease stage. The results of study 301 demonstrate a reduced decline of approximately 25% to 40% on clinical endpoints. For the primary endpoint, this corresponds to a preservation of CDR-SB by approximately 5.3 months relative to placebo over the 18 months of the study. This preservation of cognitive function is clearly clinically meaningful.

An exploratory subgroup analysis in apolipoprotein E (ApoE) ε4 homozygotes showed no treatment effect on the CDR-SB; however, there were trends for efficacy on the ADAS-Cog 14 and ADCS-ADL-MCI. There were favorable trends for treatment effects in health-related outcome measures and biomarkers in the homozygote subgroup. Overall, the data appear to suggest a treatment benefit in ApoE ε4 homozygotes although there are uncertainties about the magnitude of benefit in this subgroup relative to heterozygotes and noncarriers.

Lecanemab received accelerated approval based on data from Study 201 that demonstrated substantial evidence of effectiveness on a reasonably likely surrogate endpoint, reduction in brain amyloid beta plaques as measured by PET imaging. The results of Study 301 verify and describe the clinical benefit of lecanemab for the treatment of Alzheimer's disease. The collective evidence from Study 201 and 301 continue to demonstrate substantial evidence of effectiveness for lecanemab for the treatment of Alzheimer's disease, and support the traditional approval of lecanemab in this population. The effect on the primary endpoint represents a clinically meaningful reduction of clinical decline. The finding on the primary endpoint is supported by statistically significant results for all 4 multiplicity-controlled secondary endpoints, including endpoints capturing distinct information regarding cognitive decline. The treatment effect in Study 301 is supported by the consistently favorable results for the primary and secondary endpoints across subgroups of interest defined by demographic and baseline disease characteristics. Biomarkers reflecting target engagement, effects on downstream tau pathophysiology, and neurodegeneration support the observations on the clinical endpoints.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Alzheimer's disease is a progressive, degenerative brain disorder that affects memory, thinking, and behavior and is the most common cause of dementia. • Clinical symptoms include difficulty remembering recent conversations, names, or events, impaired communication, disorientation, confusion, poor judgment, behavioral changes, and ultimately, difficulty walking, speaking, and swallowing. • Alzheimer's disease exists on a continuum from biological changes in the brain, to subtle problems with memory and thinking, and ultimately difficulties that affect an individual's ability to perform everyday activities. The disease process may begin 20 years or more before symptoms arise. • After a diagnosis of Alzheimer's dementia, the average survival is 4 to 8 years. • An estimated 6.7 million Americans age 65 years and older are currently living with Alzheimer's disease. • Alzheimer's disease was the sixth leading cause of death in the United States in 2019. • Almost two-thirds of Americans with Alzheimer's disease are women. Older African Americans and Latinos are disproportionately more likely to have Alzheimer's disease than White Americans.	Alzheimer's disease is a major public health issue which imposes an immense burden on patients and caregivers. The number of Americans with Alzheimer's disease dementia is expected to increase significantly in the next few decades.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Current Treatment Options	• FDA-approved therapies include the acetylcholinesterase inhibitors donepezil, rivastigmine, and galantamine, and the N-methyl-D-aspartate receptor antagonist memantine. Treatment effects of these therapies are modest and transitory. • Antipsychotics are commonly prescribed to treat behavioral symptoms but are not approved for the treatment of Alzheimer's disease and are associated with increased mortality in older patients. • Aducanumab and lecanemab are amyloid beta-directed antibodies approved under the accelerated approval pathway and indicated for the treatment of Alzheimer's disease, specifically patients with mild cognitive impairment or mild dementia stage of disease.	There is an urgent and unmet medical need for effective treatments for Alzheimer's disease. In addition to the general need for more effective treatments, there is a particular unmet need for effective treatments to delay, halt, or reverse the pathophysiological processes that ultimately lead to the clinical deficits of Alzheimer's disease.
Benefit	• The efficacy of lecanemab in patients at the early stages of symptomatic Alzheimer's disease was evaluated in Study 301 ○ Participants were randomized 1:1 to receive placebo or 10 mg/kg lecanemab as an IV infusion once every two weeks. ○ The trial enrolled 1795 patients: 898 in the lecanemab treatment arm and 897 in the placebo arm. ○ The primary endpoint was the change from baseline in CDR-SB at Week 79. CDR-SB is an integrated scale that meaningfully assesses both daily function and cognitive effects. Key secondary endpoints were change from baseline to Week 79 in amyloid PET using Centiloids, ADAS-Cog 14, ADCOMS, and ADCS-ADL-MCI. ○ Exploratory endpoints included health-related quality of life measures. ○ Key pharmacodynamic endpoints included change from	The results of Study 301 confirm the clinical benefit of lecanemab for the treatment of Alzheimer's disease. The effect on the primary endpoint represents a clinically meaningful reduction of clinical decline. The finding on the primary endpoint is supported by statistically significant results for all 4 multiplicity-controlled secondary endpoints, including endpoints capturing distinct information regarding cognitive decline. The treatment effect in Study 301 is supported by the consistently favorable results for the primary and secondary endpoints across subgroups of interest defined by demographic and baseline disease characteristics. Biomarkers reflecting

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	baseline in tau PET, brain volumes as measured by volumetric MRI, and fluid biomarkers of amyloid, tau, and neurodegeneration. • Treatment with lecanemab demonstrated reduced clinical decline, as evidenced by a statistically significant treatment effect on change from baseline in CDR-SB compared to placebo (-0.45 [-27%], p=0.00005). • The lecanemab treatment arm had a statistically significant reduction in brain amyloid from baseline to Week 79 compared to the placebo arm (mean difference -59.9 Centiloid; p<0.00001). • Statistically significant treatment effects in favor or lecanemab were observed for all multiplicity-controlled secondary clinical endpoints at Week 79: ADAS-Cog 14 (-1.442 [-26%], p=0.00065), ADCOMS (-0.05, [-24%], p=0.00002), and ADCS-ADL-MCI (2.016 [-37%], p<0.0001). • Results were robust to sensitivity analyses. • Treatment effects on biomarkers reflecting brain amyloid, downstream Alzheimer's tau pathophysiology, and neurodegeneration supported the observations on clinical outcomes. • Favorable results were observed for the primary endpoint across subgroups of interest, except for homozygous ApoE ε4 carriers. Results in homozygous ApoE ε4 carriers for secondary clinical endpoints, biomarkers, and health outcome assessments, however, support a favorable treatment effect in this subgroup.	target engagement, effects on downstream tau pathophysiology, and neurodegeneration support the observations on the clinical endpoints.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk and Risk Management	• Refer to safety review by Dr. Erten-Lyons.	

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application

☒	The patient experience data that was submitted as part of the application include:			Section where discussed, if applicable
	☒	Clinical outcome assessment (COA) data, such as		[Sec 6.1 Study endpoints]
		☒	Patient reported outcome (PRO)	
		☒	Observer reported outcome (ObsRO)	
		☒	Clinician reported outcome (ClinRO)	
		☒	Performance outcome (PerfO)	
	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Natural history studies		
	☐	Patient preference studies (e.g., submitted studies or scientific publications)		
	☐	Other: (Please specify)		
☒	Patient experience data that were not submitted in the application, but were considered in this review:			
		☒	Input informed from participation in meetings with patient stakeholders	
		☐	Patient-focused drug development or other stakeholder meeting summary reports	
		☐	Observational survey studies designed to capture patient experience data	
		☐	Other: (Please specify)	
☐	Patient experience data was not submitted as part of this application.			

2. Therapeutic Context

2.1. Analysis of Condition

Alzheimer's disease is a progressive, degenerative brain disorder that affects memory, thinking,

and behavior and is the most common cause of dementia. According to a recent report (Alzheimer's Association 2023), an estimated 6.7 million Americans age 65 years and older are currently living with Alzheimer's disease dementia. The report noted that Alzheimer's disease was the sixth-leading cause of death in the United States and the fifth-leading cause of death for those age 65 years and older in 2019. Almost two-thirds of Americans with Alzheimer's disease are women. Older African Americans and Latinos are disproportionately more likely to have Alzheimer's disease than White Americans (Alzheimer's Association 2023).

Alzheimer's disease exists on a continuum from pathological changes in the brain which are undetectable to the person affected, to subtle problems with memory and thinking, and ultimately, difficulties with memory, language, problem-solving, and other skills that affect an individual's ability to perform everyday activities. The disease process may begin 20 years or more before symptoms arise (Vermunt et al. 2019). Life expectancy varies depending on many factors, but after a diagnosis of Alzheimer's dementia the average survival is 4 to 8 years (Alzheimer's Association 2023). The long duration of the disease contributes to the burden not only on the individuals with the disease, but also their families and caregivers who provide most of the patient care and are at an increased risk for emotional distress and negative mental and physical outcomes.

The two pathological hallmarks of Alzheimer's disease are extracellular deposits of Aβ plaques, and intracellular aggregates of hyperphosphorylated tau in the form of neurofibrillary tangles. Accumulation of Aβ in the brain is an important part of the disease process and precedes the accumulation of tau pathology and neural degeneration. Consequently, therapies to inhibit Aβ production or enhance Aβ clearance have been investigated in an attempt to slow or halt the disease process. Importantly, "anti-amyloid" therapies are not a distinct class of drugs, but rather reflect many different modes of action. A careful examination of anti-Aβ therapies has revealed that for therapies targeting aggregated forms of Aβ there exists a relationship between reduction of brain amyloid plaque and reduction of clinical decline such that robust reduction of brain amyloid plaque to levels consistent with a negative PET scan is associated with a reduction in clinical decline by approximately 20% to 40%.

Some anti-Aβ monoclonal antibodies, including lecanemab, have been associated with the occurrence of amyloid related imaging abnormalities (ARIA) that require special attention with respect to dosing and monitoring. ARIA covers a spectrum of imaging findings detected on brain magnetic resonance imaging (MRI) which include ARIA-edema (ARIA-E) and ARIA-hemorrhage (ARIA-H).

2.2. Analysis of Current Treatment Options

Treatment goals for patients with Alzheimer's disease are often directed to maintain quality of

life, treat cognitive symptoms, and manage behavioral and psychological symptoms of dementia. Approved Alzheimer's disease treatments include the cholinesterase inhibitors donepezil, rivastigmine, and galantamine, and the N-methyl-D-aspartate antagonist memantine. Aducanumab and lecanemab were approved using the accelerated approval pathway and are the first approved therapies to target the underlying pathology of the disease.

There remains an urgent and unmet medical need for effective treatments for Alzheimer's disease. In addition to the general need for more effective treatments, there is a particular unmet need for effective treatments to delay, halt, or reverse the pathophysiological processes that ultimately lead to the clinical deficits of Alzheimer's disease.

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Lecanemab (trade name Leqembi) received accelerated approval on January 6, 2023.

3.2. Summary of Presubmission/Submission Regulatory Activity

IND 105081 for lecanemab (previously BAN2401) was opened in the United States on June 30, 2010. For a summary of regulatory activity up to the time of the BLA submission for accelerated approval refer to the previous clinical efficacy review (Krudys, DARRTS 1/05/2023). Regulatory activity relevant to the evaluation of efficacy in this submission includes the following:

- December 17, 2021 – A Type B Meeting was held to discuss selected aspects of the analysis of efficacy data for the ongoing Study 301, including prioritization of ApoE ε4 carriers in the sequence of objectives, exclusion of subjects from the primary analysis population due to the COVID-19 pandemic, and the proposed testing hierarchy. The Division cautioned that there did not appear to be a significant advantage in prioritizing the ApoE ε4 carrier population. The Division also advised that biomarker-derived endpoints may not need to be included in the sequence of testing for efficacy outcomes and that plans to exclude subjects due to COVID-19 appeared reasonable, but may also be a matter of review.

- July 11, 2022 – A Type B Meeting was held to discuss the format and contents of a supplemental BLA. The Division agreed that a Summary of Clinical Efficacy was not necessary for this submission.

- August 15, 2022 – The Division provided advice on the statistical analysis plan. Specifically, the Division noted that the use of a Full Analysis Set for the primary analysis which excludes some randomized patients due to COVID-19 would be a matter of review because it

excludes randomized subjects. The Division also cautioned that if the proportion of intercurrent events is not low, then the estimand including data after those intercurrent events may be a matter of review.

- January 6, 2023 – Accelerated approval was granted, and the efficacy supplement to support traditional approval was submitted.

3.3. Foreign Regulatory Actions and Marketing History

Lecanemab is not approved or marketed in any foreign country.

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

OSI conducted inspections of three clinical sites. Site selection was based on risk ranking in the CDER clinical investigator site selection tool, enrollment, and prior inspections. The review concludes that Study 301 appears to have been conducted adequately, and the data generated by the sites inspected appear acceptable in support of the respective indication.

4.2. Product Quality

Please see the Office of Pharmaceutical Quality (OPQ) review for any issues related to product quality.

4.3. Clinical Microbiology

Not applicable.

4.4. Nonclinical Pharmacology/Toxicology

Please see Dr. Toscano's review of the original BLA for any issues related to nonclinical pharmacology/toxicology.

4.5. Clinical Pharmacology

The clinical pharmacology review team has concluded that the effectiveness of lecanemab was supported by the effects on brain amyloid, plasma/CSF biomarkers, and exposure-response

relationships from Study 301 and Study 201. Model based exposure-response analyses for both studies demonstrated that higher exposures to lecanemab were associated with (1) greater reduction in clinical decline on CDR-SB and ADAS-Cog 14; (2) greater reduction in amyloid beta plaque; and (3) greater increase in plasma Aβ42/40 ratio and greater reduction in plasma p-tau 181. An association between reduction in amyloid beta plaque and clinical decline on CDR-SB and ADAS-Cog 14 was also observed.

Serum lecanemab Cmax and AUC increased in an approximately dose-proportional manner within the assessed single dose range of 0.3 mg/kg to 15 mg/kg. The mean terminal t½ of lecanemab was 5 to 7 days when administered at 1 mg/kg or higher doses. Steady-state was achieved after 6 weeks of 10 mg/kg administered every 2 weeks, and the systemic accumulation was 1.4-fold based on AUC.

Based on the pop-PK modeling updated by including data from Study 301, the mean value (95% CI) for central volume of distribution at steady-state is 3.24 (3.18-3.30) L, and the clearance of lecanemab (95% CI) is 0.370 (0.353-0.384) L/day. Lecanemab is degraded by proteolytic enzymes and is not expected to undergo renal elimination or metabolism by hepatic enzymes. Sex, body weight, and albumin were found to impact exposure to lecanemab, however, none of these covariates were found to be clinically significant and no dose adjustment is recommended based on intrinsic factors.

The review team recommends including a text description in labeling regarding the subgroup findings by ApoE ε4 genotype, including clinical endpoints and biomarkers to inform the benefit risk assessment. In addition, the team recommends including labeling information about the availability of a test to determine ApoE ε4 genotype to assist decision making.

4.6. Devices and Companion Diagnostic Issues

Not applicable.

4.7. Consumer Study Reviews

Not applicable.

5. Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

One clinical study is intended to serve as the confirmatory study to verify the clinical benefit of lecanemab and is presented in Table 1. The study supporting accelerated approval is relevant

for this review and has been summarized in the clinical review of the original submission (Krudys, DARRTS 1/05/2023).

Table 1: Tabular Presentation of the Clinical Study Contributing Efficacy Data Relevant to the Verification of Clinical Benefit for this sBLA

Trial Identity/NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population (per categorization at the time of enrollment)	No. of Centers and Countries
Controlled Studies to Support Efficacy and Safety							
BAN2401-G000-301 (Study 301)/NCT03887455	Randomized, double-blind, placebo-controlled, parallel group	IV infusion over one hour Placebo Saline infusion biweekly Lecanemab 10 mg/kg biweekly	Primary Change from baseline in CDR-SB at 18 months Secondary Change from baseline in brain amyloid by PET, ADAS-Cog 14, ADCOMS, and ADCS-ADL-MCI at 18 months	18-month treatment period 3-month follow-up period Seamless enrollment in OLE with up to 4 years of treatment	1795	MCI due to Alzheimer's disease or mild Alzheimer's disease dementia CDR global score of 0.5 to 1.0 and memory box score ≥ 0.5 MMSE score ≥ 22 Positive amyloid load by PET or CSF 50 to 90 years of age	235 centers in 13 countries

5.2. Review Strategy

This review evaluates whether the results of Study 301 verify the clinical benefit of lecanemab for the treatment of Alzheimer's disease. The results of the study used to support accelerated approval, Study 201, are referenced when appropriate to provide context, but are not integrated in this review. A detailed consideration of Study 201 can be found in the review supporting accelerated approval (Krudys, DARRTS 1/05/2023).

This review focuses solely on clinical efficacy. This application is being reviewed separately for safety by Dr. Erten-Lyons.

6. Review of Relevant Individual Trials Used to Support Efficacy

6.1. Study 301 (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

6.1.1. Study Design

Overview and Objective

Study 301 was designed to evaluate the efficacy and safety of lecanemab in patients with mild cognitive impairment (MCI) due to Alzheimer's disease or mild Alzheimer's disease dementia. The primary objective was to evaluate the efficacy of lecanemab 10 mg/kg biweekly compared with placebo on the change from baseline in the CDR-SB at 18 months of treatment.

Trial Design

Study 301 was a multicenter, randomized, double-blind, placebo-controlled, parallel-group study in patients with MCI due to Alzheimer's disease or mild Alzheimer's disease dementia. A total of 235 centers across 13 countries in North America, Europe, Australia, and Asia enrolled patients into the trial. Randomization was stratified by clinical subgroups (MCI due to Alzheimer's disease or mild Alzheimer's disease dementia), ApoE ε4 carrier status (carrier or non-carrier), ongoing treatment with concurrent medications for treatment of Alzheimer's disease (yes or no), and geographical region (North America, Europe, or Asia Pacific). At least 50% of patients enrolled in the study were to be in the MCI due to Alzheimer's disease subgroup. The study included a 60-day screening period, an 18-month (78-week) placebo-controlled period, and a safety follow-up period of 3 months after the final dose. Patients were randomized to placebo or 10 mg/kg biweekly lecanemab in a 1:1 ratio in the placebo-controlled

period.

Patients who completed the placebo-controlled period and met inclusion/exclusion criteria had the option to directly enter the open-label extension (OLE) phase of the study for up to 4 years.

Diagnostic Criteria

Patients fulfilled clinical criteria for either MCI due to Alzheimer's disease or mild Alzheimer's disease dementia as defined by the 2011 National Institute on Aging-Alzheimer's Association (NIA-AA) framework (Albert et al. 2011; McKhann et al. 2011) and were required to have evidence of brain Aβ pathology by either visual read of a PET scan or CSF assessment of t-tau/$A\beta_{1-42}$.

Key Inclusion Criteria

1. Objective impairment in episodic memory as indicated by at least 1 standard deviation below age-adjusted mean in the Wechsler-Memory Scale-IV Logical Memory (subscale) II (WMS-IV LMII), as follows:
    a. ≤15 for age 50 to 64 years
    b. ≤12 for age 65 to 69 years
    c. ≤11 for age 70 to 74 years
    d. ≤9 for age 75 to 79 years
    e. ≤7 for age 80 to 90 years
2. CDR global score of 0.5 or 1.0 with a Memory Box score of 0.5 or greater
3. Male or female patients age 50 to ≤90 years
4. Positive amyloid pathology by either visual read of PET or CSF assessment
5. Mini-Mental State Examination (MMSE) score ≥22
6. Patients receiving cholinesterase inhibitors or memantine or both must be on stable dose for at least 12 weeks
7. Must have a caregiver/informant who spends at least 8 hours per week with the patient and is available for the duration of the study

Key Exclusion Criteria

1. Any neurological condition (other than Alzheimer's disease) which may be contributing to cognitive impairment
2. History of transient ischemic attacks, stroke, or seizures within the previous year of screening
3. Any psychiatric diagnosis or symptoms that could interfere with study procedures
4. Geriatric Depression Score ≥8
5. Contraindications to MRI scanning

6. Evidence of clinically significant lesions on brain MRI that could indicate a dementia diagnosis other than Alzheimer's disease
7. Brain MRI performed at screening that shows evidence of any of the following: more than 4 microhemorrhages (defined as 10 mm or less at the greatest diameter), a single macrohemorrhage greater than 10 mm at greatest diameter, an area of superficial siderosis, vasogenic edema, cerebral contusion, encephalomalacia, aneurysms, vascular malformations, infective lesions, multiple lacunar infarcts or stroke involving a major vascular territory, severe small vessel, or white matter disease or space occupying lesions or brain tumors
8. Any immunological disease which is not adequately controlled or requires treatment with biological drugs
9. Bleeding disorder that is not under control
10. Any medical condition which is not stably and adequately controlled, or which in the opinion of the investigator could affect the subject's safety or interfere with study assessments
11. Participation in a clinical study involving any new chemical entities for Alzheimer's disease within 6 months of screening unless it can be documented that the subject was randomized to placebo
12. Known prior exposure to lecanemab

Reviewer Comment: The patient population is consistent with Stage 3 and Stage 4 patients as described in the FDA 2018 Guidance for Industry Early Alzheimer's Disease: Developing Drugs for Treatment and is largely similar to the population enrolled in Study 201.

Dose Selection

Selection of the 10 mg/kg biweekly dosing regimen was based on the results of Study 201 (see Krudys, DARRTS 1/05/2023).

Study Treatments

IV infusions of lecanemab or placebo were administered over approximately 60 minutes. Dosing occurred every two weeks over a period of 76 weeks for a total of 39 doses.

In response to the COVID-19 pandemic, home infusions were allowed according to the applicant's approval and local guidelines for patients who could not visit the clinical site to receive treatment. Home infusions for visits with clinical endpoint assessments were to be avoided if possible and home infusion of the first dose was not allowed.

All patients in the OLE received open-label lecanemab biweekly.

Assignment to Treatment

An interactive voice and web response system (IxRS) was used to manage randomization and treatment assignment. Randomization was stratified by clinical subgroups (MCI due to Alzheimer's disease or mild Alzheimer's disease dementia), ApoE ε4 carrier status (carrier or non-carrier), ongoing treatment with concurrent medications for treatment of Alzheimer's disease (yes or no), and geographical region (North America, Europe, or Asia Pacific). Enrollment was monitored such that at least 50% of patients enrolled in the study were to be in the MCI due to Alzheimer's disease subgroup.

Blinding

Study drug was dispensed by an unblinded pharmacist at each site. All other study site staff and patients were blinded to treatment assignment during the placebo-controlled period. The clinicians responsible for rating clinical assessments were not to be involved in patient care or management and were to remain blinded to results of safety assessments, including MRI, laboratory assessments, and adverse events (AEs). An independent, blinded medical monitoring team reviewed ARIA, infusion-related reactions, and hypersensitivity reactions.

Dose Modification/Dose Discontinuation

Study drug was temporarily interrupted for the following:

- Evidence of symptomatic or radiographically moderate or severe amyloid-related imaging abnormalities-edema (ARIA-E)
- Development of any of the following categories of amyloid-related imaging abnormalities-hemorrhage (ARIA-H): a single macrohemorrhage (>10 mm at greatest diameter), multiple (>10) cerebral microhemorrhages cumulatively, symptomatic cerebral microhemorrhages, or symptomatic superficial siderosis

Upon resolution/stabilization of the event, the patient resumed drug treatment for the remainder of the study. If a third event occurred, the patient was discontinued from study drug. For patients who paused dosing due to more than 10 cerebral microhemorrhages, study drug was discontinued if further new microhemorrhages developed after resumption of treatment.

Study drug was discontinued if any of the following were observed:

- Infusion or injection reactions of Grade 3 severity or above that did not lessen or resolve with treatment
- Clinical features which indicate meningoencephalitis
- Hypersensitivity reactions with clinical features of tissue injury

- Severe ARIA-E associated with a serious adverse event (SAE)

Administrative Structure

An independent Data Safety Monitoring Board (DSMB) was established to periodically review safety data and advise the applicant on issues relevant to safety. Members of the committee included up to three clinicians with experience in the management of patients with Alzheimer's disease and one statistician.

A separate vendor was used for rater training, qualification, and central review of clinical scale administration and scoring.

Procedures and Schedule

The schedule of key assessments is provided in Table 2. The pre-randomization period was to consist of screening and baseline visits within a 60-day period before administration of the first dose at the Week 1 visit. An extension of up to 90 days was allowed under extenuating circumstances, specifically the COVID-19 pandemic. Study visits occurred every 2 weeks for 78 weeks with a follow-up visit 3 months after the last dose of the study drug.

Table 2: Study 301 Schedule of Key Assessments

Assessment	**Schedule**
Eligibility Criteria	Screening and Baseline
ApoE Genotyping	Screening
Physical Examination	Screening, Baseline, Weeks 9, 17, 27, 39, 53, 65, 79, Follow-up, Early Termination
Safety Brain MRI	Screening, Weeks 9, 13, 27, 53, 79, Follow-up, Early Termination
Study Drug Administration	Weeks 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77
Anti-Lecanemab Ab	Weeks 1, 5, 13, 27, 39, 53, 65, 77, Follow-up, Early Termination
Lecanemab Concentration	Weeks 1, 5, 13, 27, 39, 53, 65, 77, Follow-up, Early Termination
Blood for Biomarker Analysis	Weeks 1, 27, 53, 77, 79, Early Termination
CSF Collection (optional)	Baseline, Weeks 53, 77, Early Termination
Amyloid PET (optional)	Baseline, Weeks 13, 27, 53, 79, Early Termination
Tau PET (optional)	Baseline, Weeks 57, 79, Early Termination
Volumetric MRI	Screening, Weeks 9, 13, 27, 53, 79, Early Termination
MMSE, CDR	Screening, Baseline, Weeks 13, 27, 39, 53, 65, 79, Follow-up, Early Termination
ADAS-Cog14	Baseline, Week 13, 27, 39, 53, 65, 79, Follow-up, Early Termination

ADCS-ADL-MCI	Baseline, Weeks 27, 53, 79, Follow-up, Early Termination
EQ-5D-5L, QOL-AD, Zarit Burden Interview	Baseline, Weeks 27, 53, 79, Follow-up, Early Termination

Created by reviewer, modified from Tables 8, 9, and 10 in Study 301 protocol

Concurrent Medications

Treatment of Alzheimer's disease with cholinesterase inhibitors and/or memantine was allowed if patients were on a stable dose for at least 12 weeks prior to Baseline. During the study, patients could initiate these medications or modify their doses if deemed medically necessary. Patients taking other medications were required to be on stable doses for at least 4 weeks before Baseline.

The following restrictions and limitations were also implemented in the protocol:

- Immunoglobulins, monoclonal antibodies, and plasmapheresis were not permitted for a period of 6 months before Baseline until the Follow-up visit
- Patients on anticoagulants were required to have their anticoagulation status optimized and stable for at least 4 weeks before Screening
- Thrombolytics were allowed, but treatment with study drug was temporarily suspended until stabilization or resolution of the medical condition requiring thrombolytic drug treatment
- Systemic immunosuppressive drugs were not permitted 3 months before Baseline until the Follow-up visit
- Cognitive assessments were not to be performed within 72 hours after administration of a sedative

Subject Completion, Discontinuation, or Withdrawal

Patients who completed the Week 79 visit were considered to have completed the study.

Patients who discontinued the study or study drug were to have an early termination visit within 7 days after the last dose of study drug and the 3-month follow-up visit. The clinical assessments to be conducted at the early termination visit include those outlined in Table 2. Patients who discontinued study drug were to return for each scheduled visit when clinical assessments of efficacy were to be conducted. Drug specific reactions that led to protocol-driven discontinuation include ARIA, infusion reactions, and hypersensitivity reactions as described earlier. Reasons for study discontinuation captured by the case report form (CRF) include AEs, lost to follow-up, subject choice, withdrawal of consent, pregnancy, inadequate therapeutic effect, study termination by the sponsor, or other.

Patients withdrawn from the study were not replaced.

Study Endpoints

Primary Efficacy Endpoint

The primary efficacy endpoint was the change from baseline in CDR-SB at Week 79. The CDR-SB assesses three domains of cognition (memory, orientation, judgment/problem solving) and three domains of function (community affairs, home/hobbies, personal care) using semi-structured interviews with the patient and a reliable companion or informant. A qualified rater uses interview data and clinical judgment to assign scores for each domain ranging from none=0, questionable = 0.5, mild = 1, moderate = 2 to severe = 3. The personal care domain does not include the 0.5 score. Scores from each domain are summed to provide the CDR-SB value ranging from 0 to 18, with higher scores indicating greater disease severity. CDR-SB has been described in the literature (Cederbaum et al. 2013) as a suitable primary endpoint for clinical trials in patients with early Alzheimer's disease due to its psychometric properties and its ability to assess both cognitive and functional disability. CDR-SB is accepted by FDA as an acceptable primary outcome assessment for studies of Alzheimer's disease in early stages of the disease that are intended to demonstrate substantial evidence of effectiveness. It has been widely used as the primary efficacy endpoint in clinical trials for other investigational drugs in this population. A global score ranging from 0 to 3 is also generated as part of the assessment. The applicant conducted an exploratory analysis for the time to worsening on the CDR global score, defined as an increase from baseline by at least 0.5 points on two consecutive scheduled visits in which the CDR global score was assessed.

CDR-SB assessments were conducted by a clinician not involved in patient care or management who remained blinded to treatment assignment and results of safety assessments. All sites were asked to maintain the same rater throughout the study. A contract research organization (CRO), (b) (4), was selected to manage rater training, rater qualification, and central review of clinical assessment and scoring. Assessments were reviewed by central readers.

Reviewer Comment: CDR-SB is an integrated scale that adequately and meaningfully assesses both daily function and cognitive effects in early Alzheimer's disease and is consistent with FDA guidance on clinical endpoints in Stage 3 patients. The distinction between cognitive and functional domains for the CDR-SB is somewhat artificial because the effects on cognition are measured in a way that reflect impact on function and are clinically meaningful.

Secondary Clinical Endpoints

ADAS-Cog

The ADAS-Cog is a cognitive assessment consisting of clinical ratings and cognitive tasks that was originally developed for use in clinical trials of patients with later stages of Alzheimer's disease dementia. ADAS-Cog 11 includes 11 tasks measuring disturbances of memory, language, and praxis. Many of the items of the ADAS-Cog 11 are at the measurement floor in patients with mild disease and may not show decline over the length of a typical clinical trial. Therefore, three additional tasks were added to create the ADAS-Cog 14 for use in this earlier disease population. The ADAS-Cog 14 scale ranges from 0 to 90, with higher scores indicating greater disease severity.

ADCS-ADL-MCI

The ADCS-ADL-MCI is a questionnaire for informants that consists of 17 instrumental items and 1 basic item (getting dressed) intended to reflect activities of daily living. Informants are asked whether the patient attempted each item during the prior 4 weeks and their level of performance. Responses are "Yes," "No," or "Don't Know" with additional sub-ratings depending on the item. The total score ranges from 0 to 53 with lower scores indicating greater impairment. The ADCS-ADL-MCI was adapted from the ADCS-ADL, which was developed for a population with more advanced disease and served as a key endpoint in many of the acetylcholinesterase trials.

ADCOMS

The Alzheimer's Disease Composite Score (ADCOMS) is a weighted linear combination of selected items from 3 commonly used scales: 4 items from the ADAS-Cog (delayed word recall, orientation, word recognition, and word finding), two items from the MMSE (orientation to time and drawing), and all 6 items from the CDR-SB. MMSE is a widely used performance-based assessment of cognitive ability consisting of 11 tasks evaluating orientation, word recall, attention and calculation, and visuospatial functions. ADCOMS scores range from 0 to 1.97 with a higher composite score indicating greater disease severity. ADCOMS was developed to provide an assessment more sensitive to change and treatment effects in patients at the early stages of disease (Wang et al. 2016).

The clinicians responsible for rating ADAS-Cog 14 and MMSE were not to be involved in patient care or management and were to remain blinded to results of safety assessments, including MRI, laboratory assessments, and AEs. All sites were asked to maintain the same raters for the secondary clinical endpoints throughout the study. No one rater was to perform all clinical assessments at a study visit. There was also central review of ratings for MMSE and ADAS-Cog 14.

Reviewer Comment: These measures capture symptoms and impacts of Alzheimer's disease that are meaningful to patients and are appropriate selections for use in supporting an effect on an acceptable primary measure.

Exploratory Health-Related Quality of Life Assessments

The following health-related quality of life assessments were included as exploratory endpoints:

- European Quality of Life-5 Dimensions 5-Level version (EQ-5D-5L) is a measure of health-related quality of life that covers 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). The assessment was completed by the patient, the care partner as a proxy of the patient, and by the care partner.
- Quality of Life in Alzheimer's Disease (QOL-AD) is an interview with 13 questions specifically interrogating the general quality of life for patients with Alzheimer's disease. The assessment was completed by the patient and the care partner as a proxy of the patient.
- The Zarit Burden Interview is a 22-item instrument to specifically assess the challenges experienced by care partners of individuals with Alzheimer's disease.

Pharmacodynamic Endpoints

Key biomarker and pharmacodynamic (PD) endpoints included the following:

- Change from baseline in amyloid signal as measured by PET and quantified by a composite standardized uptake value ratio (SUVR) for a composite cortical region of interest with whole cerebellum mask as a reference region. For patients enrolled in the longitudinal amyloid PET substudy, the same tracer (florbetapen, florbetapir, or flutemetamol) was used for baseline and follow-up assessments. SUVR values were converted to the Centiloid scale (Klunk et al. 2015) to allow for harmonization across tracers. Change from baseline in brain amyloid plaque was listed as the first key secondary endpoint in the protocol and was formally included in the statistical testing sequence.
- Change from baseline in tau PET as measured by ^{18}F-MK-6240 PET and quantified by a composite SUVR. The SUVR was calculated for the following regions: temporal, medial temporal, meta-temporal, occipital, parietal, cingulate, frontal, and whole cortical gray matter. A measurement of global tau load (Tau^{IQ}) was also assessed.
- Change from baseline in CSF levels of $A\beta_{1\text{-}40}$, $A\beta_{1\text{-}42}$, phosphorylated tau at residue 181 (p-tau 181), total tau (t-tau), neurofilament light chain (NfL), and neurogranin.
- Change from baseline in plasma levels of $A\beta_{42/40}$, p-tau 181, NfL, and glial fibrillary acidic protein (GFAP).

- Change from baseline in brain volumes as measured by volumetric magnetic resonance imaging (vMRI) for the following regions: total hippocampal, left hippocampal, right hippocampal, whole brain, lateral ventricular, and cortical thickness.

Statistical Analysis Plan

The original Statistical Analysis Plan (SAP) was issued on April 9, 2019, and was amended once, with the final version implemented on September 6, 2022, prior to study completion.

Sample Size Determination

Based on results of Study 201, the sample size calculation assumed a standard deviation of change from baseline in CDR-SB at 18 months of 2.031, a treatment difference of 0.373, and a dropout rate of 20%. Under these assumptions, a total sample size of 1566 subjects had 90% power to detect the treatment difference using a 2-sample t-test at a significance level of 2-sided alpha = 0.05. The sample size was increased during the study by approximately 200 subjects to account for the approximately 200 subjects who missed 3 or more consecutive doses, presumably due to restrictions implemented in response to the COVID-19 pandemic.

Interim Analyses

Interim analyses for efficacy were not performed.

Definitions of Statistical Analysis Populations

The applicant defined two populations for the primary efficacy analysis depending on the regulatory authority: the ITT Full Analysis Set (FAS+) for the European Medicines Agency (EMA) and Japanese Ministry of Health, Labor and Welfare (MHLW)/PMDA and the ITT FDA Full Analysis Set (ITT FDA FAS) for the FDA and other global authorities. The definitions of these analysis populations and others are as follows:

- Randomized Set – all patients who were randomized to study drug

- ITT Full Analysis Set (FAS+) – randomized patients who received at least one dose of study drug and who had a baseline assessment and at least one post-dose primary efficacy measurement

- ITT FDA Full Analysis Set (FDA FAS) – randomized patients who received at least one dose of study drug, had a baseline assessment and at least one post-dose primary efficacy measurement, and were not randomized on or before the end date of the

dosing hold at the sites which had dosing holds of 6 or more weeks (≥42 days, which is equal to 3 consecutive doses)

- Per Protocol (PP) Analysis Set – subset of patients in the ITT FDA FAS who did not miss 3 or more consecutive doses during their first 6 months of the study

- Pharmacodynamic (PD) Analysis Sets – patients who had received at least one dose of study drug and who had baseline and at least one post-dose assessment for the PD endpoint. Each PD endpoint had its own analysis set.

Analysis Method for Primary Endpoint

A mixed model repeated measures (MMRM) model was used to analyze change from baseline in CDR-SB at 18 months with baseline CDR-SB as a covariate and treatment group, visit, clinical subgroup (MCI due to Alzheimer's disease or mild Alzheimer's disease dementia), use of AD medication at baseline (yes or no), ApoE ε4 carrier status (carrier or non-carrier), geographical region (North America, Europe, or Asia Pacific), baseline CDR-SB-by-visit, and treatment group-by-visit interactions as fixed effects. All observed data were included in the analysis, including data collected after intercurrent events.

Adjustments for Multiplicity

Each statistical test was performed at a significance level of two-sided alpha = 0.05. Tests for secondary endpoints were only performed if the preceding test was statistically significant. Key secondary endpoints were tested in the following order: (1) change from baseline in amyloid PET (Centiloids) at 18 months, (2) change from baseline in ADAS-Cog 14 at 18 months, (3) change from baseline in ADCOMS at 18 months, and (4) change from baseline in ADCS-ADL-MCI at 18 months.

Missing Data

For the MMRM analysis, missing data were assumed to be missing at random. Different assumptions for missing data were explored as part of sensitivity analyses.

Subgroup Analyses

Subgroup analyses for the clinical and biomarker endpoints were planned for the following subgroups:

- Age group (<65 years, 65-74 years, and ≥75 years)
- Sex (male, female)

- Ethnicity (Hispanic-Latino, not Hispanic-Latino)
- Race (White, Black or African American, Asian, Other)
- Geographical region (North America, Europe, Asia Pacific)
- Clinical subgroup (MCI due to Alzheimer's disease, mild Alzheimer's disease dementia)
- ApoE ε4 carrier status (carrier, non-carrier)
- ApoE ε4 genotype (homozygous carriers, heterozygous carriers, non-carriers)
- Use of Alzheimer's disease medication at baseline (yes, no)

Protocol Amendments

The original protocol was issued on January 28, 2019, and was amended 10 times. Protocol Amendment 5 in March of 2020 allowed home infusion as an option at selected sites and Protocol Amendment 6 in June of 2020 added options for sites to perform remote clinical assessments if patients were unable to return to the study site. Protocol Amendment 7 increased the sample size by 200 patients in response to the COVID-19 pandemic. In February of 2022, the ADCS-ADL-MCI was moved from an exploratory endpoint to a key secondary endpoint and the FAS+ and FDA FAS analysis populations were established.

6.1.2. Study Results

Compliance with Good Clinical Practices

The applicant attests that the study was conducted in accordance with GCP and 21 CFR parts 50, 56 and 312.

Financial Disclosure

The applicant has adequately disclosed financial interests or agreements with clinical investigators as outlined in the guidance for industry Financial Disclosures by Clinical Investigators. There were 13 investigators at sites in Japan with disclosable financial interests or arrangements, but those sites do not have the potential to influence the overall results because of the low numbers of patients enrolled.

Patient Disposition

A total of 5967 patients were screened for entry into the study and 1795 patients were randomized. The most common reason for screen failure was failure to meet inclusion or exclusion criteria. Patient disposition is summarized in Table 3. All patients who were randomized received at least one dose of study drug. A total of 61 patients received study drug but were not included in the FAS+ population due to missing post-baseline efficacy

assessments. The distribution of the reasons for discontinuation between the arms was similar with the exception of more patients in the lecanemab treatment arm discontinuing treatment or study due to adverse events. Only 16 patients in the study discontinued for reasons related to COVID-19.

Table 3: Study 301 Patient Disposition

Disposition	**Study 301**	
No. of patients screened	5967	
No. of patients not randomized	4172	
	Lecanemab N=898 n (%)	**Placebo N=897 n (%)**
Patients randomized	898	897
FAS+ population	859 (95.7%)	875 (97.5%)
FDA FAS population	833 (92.8%)	833 (92.9%)
Per protocol population	730 (81.3%)	799 (89.1%)
PD Analysis Set (amyloid PET)	363 (40.4%)	353 (39.4%)
PD Analysis Set (tau PET)	135 (15.0%)	122 (13.6%)
PD Analysis Set (plasma)	847 (94.3%)	852 (95.0%)
PD Analysis Set (CSF)	142 (15.8%)	139 (15.5%)
PD Analysis Set (vMRI)	805 (89.6%)	825 (92.0%)
Discontinued treatment	199 (22.2%)	156 (17.4%)
Adverse event	69 (7.7%)	29 (3.2%)
Consent withdrawn	69 (7.7%)	71 (7.9%)
Subject choice	33 (3.7%)	28 (3.1%)
Other reasons	28 (3.1%)	28 (3.1%)
Discontinued study	169 (18.8%)	140 (15.6%)
Adverse event	51 (5.7%)	28 (3.1%)
Consent withdrawn	69 (7.7%)	67 (7.5%)
Subject choice	26 (2.9%)	24 (2.7%)
Lost to follow-up	4 (0.4%)	5 (0.6%)
Other reasons	19 (2.1%)	16 (1.8%)

Created by the reviewer using Table 14.1.1.3.1, Table 14.1.1.4.1, and Table 5 in Study 301 CSR

Due to disruptions in study drug administration during the peak of the COVID-19 pandemic, the applicant approached the Division in December 2020 about limiting the primary analysis population based on the number of consecutive missed doses. The Division responded that exclusion of patients should use only baseline information (e.g., site location and randomization date). Based on this advice, the applicant subsequently proposed in December 2021 to exclude patients from sites that were closed or on hold for 6 or more weeks between the COVID-19 pandemic peak of March 1, 2020, and July 31, 2020. As a result, a total of 68 patients (26 in the lecanemab treatment arm and 42 in the placebo arm) from 19 sites were excluded from the FAS+ population when defining the FDA FAS population.

Reviewer Comment: Excluding patients from the primary analysis based on site and randomization date was a somewhat crude attempt to address the potential for missed doses due to the COVID-19 pandemic. Ultimately, only 26 patients treated with lecanemab were excluded. A plot of the change from baseline in amyloid plaque in lecanemab treated patients who were excluded revealed a reduction that was generally consistent with the overall population. The choice of the FAS+ or FDA FAS population does not meaningfully affect the interpretation of the clinical efficacy results. For completeness, results for primary and secondary clinical endpoints using both analysis population sets will be presented. The FAS+ analysis is appropriate for labeling because it is more complete and is consistent with the typical analytical approach.

In general, ≤1% of clinical endpoint assessments were performed remotely at each study visit, with only 6 CDR-SB assessments performed remotely at the Week 79 visit.

Reviewer Comment: The inclusion of remote assessments is unlikely to affect the estimation or interpretation of treatment effects.

Protocol Violations/Deviations

Important protocol deviations were observed in 197 (11%) patients in the study (102 in the lecanemab treatment arm and 95 in placebo). The most common deviation was 4 or missed consecutive visits in 60 (6.7%) of patients in the placebo arm and 53 (5.9%) patients in the lecanemab arm. Most of these missed visits were due to COVID-19. Missed doses in the lecanemab treatment arm could make it more difficult to observe a treatment effect. Other important protocol deviations were infrequent and generally balanced between the arms. Notably, there were only 2 reported cases of the CDR rater being unblinded to safety MRI or AE data in the lecanemab treatment arm.

Table of Demographic Characteristics

Table 4 contains important information regarding demographic characteristics for each treatment arm in the FAS+ population. Demographic characteristics were balanced across the treatment arms and generally representative of the patient population except for an under-representation of African American patients. Overall, 52% of patients were enrolled in the United States.

Table 4: Study 301 Baseline Demographics (FAS+ Population)

	Placebo N=875 n(%)	Lecanemab N=859 n(%)	Total N=1734 n(%)
Sex			
Male	411 (47.0%)	416 (48.4%)	827 (47.7%)
Female	464 (53.0%)	443 (51.6%)	907 (52.3%)
Age			
Mean (SD)	71.0 (7.8)	71.4 (7.9)	71.2 (7.8)
Median (min, max)	72.0 (50.0, 90.0)	72.0 (50.0, 90.0)	72.0 (50.0, 90.0)
Age Group			
>=75 years	316 (36.1%)	325 (37.8%)	641 (37.0%)
>=65, <75 years	381 (43.5%)	368 (42.8%)	749 (43.2%)
<65 years	178 (20.3%)	166 (19.3%)	344 (19.8%)
Race			
White	677 (77.4%)	655 (76.3%)	1332 (76.8%)
Black or African American	24 (2.7%)	20 (2.3%)	44 (2.5%)
Asian	148 (16.9%)	147 (17.1%)	295 (17.0%)
Missing	12 (1.4%)	16 (1.9%)	28 (1.6%)
Other[1]	12 (1.4%)	21 (2.4%)	33 (1.9%)
American Indian or Alaskan Native	2 (0.2%)		2 (0.1%)
Ethnicity			
Not Hispanic or Latino	743 (84.9%)	715 (83.2%)	1458 (84.1%)
Hispanic or Latino	108 (12.3%)	107 (12.5%)	215 (12.4%)
Missing	24 (2.7%)	37 (4.3%)	61 (3.5%)
Region			
North America	516 (59.0%)	514 (59.8%)	1030 (59.4%)
Europe	213 (24.3%)	204 (23.7%)	417 (24.0%)
Asia-Pacific	146 (16.7%)	141 (16.4%)	287 (16.6%)
Country			
United States	455 (52.0%)	454 (52.9%)	909 (52.4%)
Canada	61 (7.0%)	60 (7.0%)	121 (7.0%)
United Kingdom	23 (2.6%)	23 (2.7%)	46 (2.7%)
Italy	43 (4.9%)	33 (3.8%)	76 (4.4%)
Spain	71 (8.1%)	67 (7.8%)	138 (8.0%)
France	24 (2.7%)	37 (4.3%)	61 (3.5%)
Germany	19 (2.2%)	16 (1.9%)	35 (2.0%)
Sweden	16 (1.8%)	13 (1.5%)	29 (1.7%)
Russian Federation	2 (0.2%)	3 (0.3%)	5 (0.3%)
Japan	64 (7.3%)	87 (10.1%)	151 (8.7%)
Korea, Republic of	75 (8.6%)	48 (5.6%)	123 (7.1%)
Singapore	7 (0.8%)	6 (0.7%)	13 (0.7%)
Australia	15 (1.7%)	12 (1.4%)	27 (1.6%)

Created by the reviewer using adsl.xpt

[1] Data on race and/or ethnicity were not collected because of local regulations.

Other Baseline Characteristics (disease characteristics, important concomitant drugs)

Table 5 contains a summary of key baseline disease characteristics and baseline use of concomitant Alzheimer's disease medications. Disease characteristics are balanced between treatment arms and reflect a population early in the course of Alzheimer's disease. The percentage of the population who were ApoE ε4 carriers is consistent with other studies in this population. Most patients were receiving concomitant medications for Alzheimer's disease and 2.8% reported receiving prior treatment with Alzheimer's disease medications.

Table 5: Study 301 Baseline Disease Characteristics (FAS+ Population)

	Placebo N=875 n(%)	Lecanemab N=859 n(%)	Total N=1734 n(%)
Baseline Clinical Stage			
MCI	544 (62.2%)	528 (61.5%)	1072 (61.8%)
Mild AD	331 (37.8%)	331 (38.5%)	662 (38.2%)
Laboratory ApoE4 status			
Carrier	600 (68.6%)	592 (68.9%)	1192 (68.7%)
Heterozygote	468 (53.3%)	456 (43.1%)	924 (53.3%)
Homozygote	132 (15.1%)	136 (15.8%)	268 (15.5%)
Noncarrier	275 (31.4%)	267 (31.1%)	542 (31.3%)
Number of Years Since Diagnosis of AD			
Mean (SD)	1.3 (1.5)	1.4 (1.5)	1.4 (1.5)
Median (min, max)	0.8 (0.0, 11.2)	0.8 (0.0, 10.0)	0.8 (0.0, 11.2)
Missing	2.0 (0.2%)		2.0 (0.1%)
Concomitant AD Medication			
No	407 (46.5%)	412 (48.0%)	819 (47.2%)
Yes	468 (53.5%)	447 (52.0%)	915 (52.8%)
Baseline CDR-SB			
Mean (SD)	3.2 (1.3)	3.2 (1.3)	3.2 (1.3)
Median (min, max)	3.0 (0.5, 8.5)	3.0 (0.5, 8.0)	3.0 (0.5, 8.5)
Baseline CDR global score			
0.5	706 (80.7%)	694 (80.8%)	1400 (80.7%)
1	169 (19.3%)	165 (19.2%)	334 (19.3%)
Baseline MMSE			
Mean (SD)	25.6 (2.2)	25.5 (2.2)	25.6 (2.2)
Median (min, max)	25.0 (22.0, 30.0)	25.0 (22.0, 30.0)	25.0 (22.0, 30.0)
Baseline ADAS-cog 14			
Mean (SD)	24.4 (7.6)	24.5 (7.1)	24.4 (7.3)
Median (min, max)	24.0 (5.0, 60.7)	24.3 (4.7, 47.7)	24.3 (4.7, 60.7)
Missing	2.0 (0.2%)	3.0 (0.3%)	5.0 (0.3%)
Baseline ADCS ADL-MCI			
Mean (SD)	40.9 (6.9)	41.2 (6.6)	41.1 (6.8)
Median (min, max)	42.0 (12.0, 53.0)	42.0 (13.0, 53.0)	42.0 (12.0, 53.0)
Missing	53.0 (6.1%)	51.0 (5.9%)	104.0 (6.0%)

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Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Compliance, defined as the total number of infusions patients received divided by the total number of infusions patients could have received, was high in both treatment arms with mean values of 96% and 94% in the placebo and lecanemab arms, respectively. The mean duration of treatment was 16.5 months in the placebo arm and 15.7 months in the lecanemab arm. The

mean cumulative dose in the lecanemab treatment arm was 334 mg/kg (out of a maximum of 390 mg/kg) and 61% of patients received ≥37 of the possible 39 infusions.

Overall, 7.3% of study participants started a new concomitant Alzheimer's disease medication at some point during the study and 5.7% changed the dose of an existing Alzheimer's disease medication. The percentages were similar in the placebo and lecanemab treatment arms.

Efficacy Results – Primary Endpoint

The primary efficacy endpoint analysis, change from baseline in CDR-SB at Week 79, demonstrated a statistically significant treatment effect in the lecanemab treatment arm compared to placebo in the FAS+ population (-0.45[-27%], p=0.00005) and the FDA FAS population (-0.39[-25%], p=0.0004) (Table 6). Nominal statistical significance was reached by Week 27 and maintained through Week 79 (Figure 1).

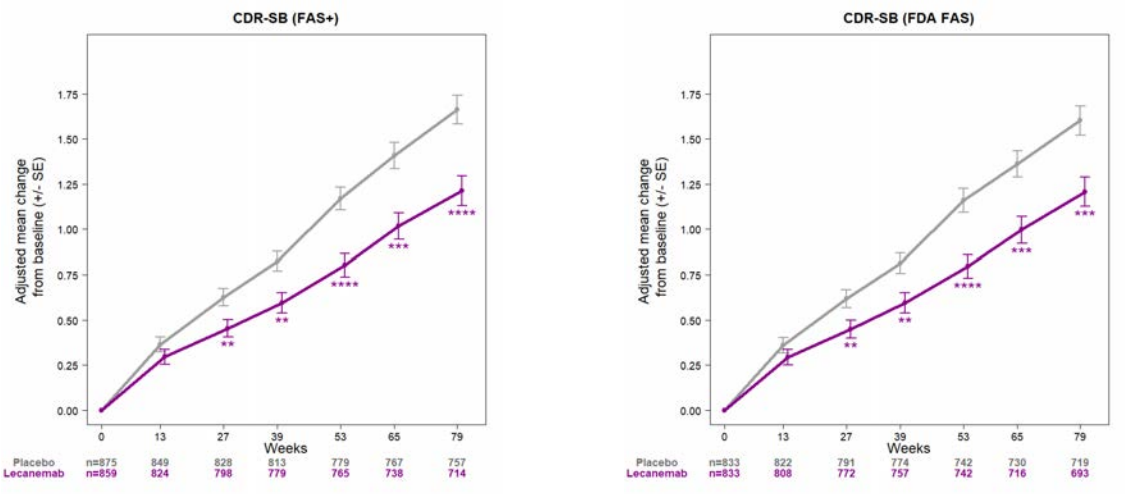
Table 6: Study 301 Primary Endpoint Analysis

	FAS+		FDA FAS	
	Placebo (N=875)	**Lecanemab** (N=859)	**Placebo** (N=833)	**Lecanemab** (N=833)
Baseline CDR-SB				
n	875	859	833	833
Mean	3.22	3.17	3.21	3.17
Change from Baseline in CDR-SB at Week 13				
n	849	824	822	808
Adjusted mean	0.364	0.296	0.359	0.292
Standard error	0.042	0.042	0.043	0.043
Difference from placebo		-0.067		-0.066
95% CI for difference		(-0.170, 0.035)		(-0.171, 0.039)
% difference vs. placebo		-19%		-18%
p-value (compared with placebo)		0.19762		0.21649
Change from Baseline in CDR-SB at Week 27				
n	828	798	791	772
Adjusted mean	0.626	0.454	0.617	0.448
Standard error	0.048	0.048	0.050	0.050
Difference from placebo		-0.172		-0.169
95% CI for difference		(-0.294, -0.049)		(-0.295, -0.044)
% difference vs. placebo		-27%		-27%
p-value (compared with placebo)		0.00594		0.00818
Change from Baseline in CDR-SB at Week 39				
n	813	779	774	757
Adjusted mean	0.824	0.595	0.813	0.594
Standard error	0.055	0.056	0.057	0.057

Difference from placebo		-0.228		-0.220
95% CI for difference		(-0.372, -0.084)		(-0.367, -0.072)
% difference vs. placebo		-28%		-27%
p-value (compared with placebo)		0.00195		0.00352
Change from Baseline in CDR-SB at Week 53				
n	779	765	742	742
Adjusted mean	1.169	0.802	1.160	0.796
Standard error	0.063	0.064	0.065	0.065
Difference from placebo		-0.366		-0.363
95% CI for difference		(-0.533, -0.199)		(-0.535, -0.192)
% difference vs. placebo		-31%		-31%
p-value (compared with placebo)		0.00001		0.00003
Change from Baseline in CDR-SB at Week 65				
n	767	738	730	716
Adjusted mean	1.408	1.018	1.362	0.997
Standard error	0.073	0.074	0.074	0.074
Difference from placebo		-0.390		-0.365
95% CI for difference		(-0.586, -0.193)		(-0.562, -0.168)
% difference vs. placebo		-28%		-27%
p-value (compared with placebo)		0.00010		0.00028
Change from Baseline in CDR-SB at Week 79				
n	757	714	719	693
Adjusted mean	1.663	1.213	1.603	1.208
Standard error	0.080	0.082	0.081	0.082
Difference from placebo		-0.451		-0.394
95% CI for difference		(-0.669, -0.233)		(-0.613, -0.176)
% difference vs. placebo		-27%		-25%
p-value (compared with placebo)		0.00005		0.00040

Source: Tables 14.2.1.1.1, 14.2.1.1.2, 14.2.1.2.5, and 14.2.1.2.6 from Study 301 CSR

Figure 1: Study 301 Longitudinal Change from Baseline for CDR-SB (left – FAS+, right – FDA FAS)



Created by the reviewer
Source: Tables 14.2.1.1.1, 14.2.1.1.2, 14.2.1.2.5, and 14.2.1.2.6 from Study 301 CSR
*p<0.05, **p<0.01, ***p<0.001. ****p<0.0001

Several prespecified sensitivity analyses demonstrated that the statistically significant results were robust to different analysis populations and modeling assumptions (Table 7). Notably, the distribution of the change from baseline in CDR-SB appeared to be skewed, with a small percentage of patients having relatively large increases. There was a total of 24 patients (17 in the placebo arm and 7 in the lecanemab treatment arm) with rapid progression, defined by the reviewer as an increase in CDR-SB of >8 by 18 months. A sensitivity analyses using log-transformed data demonstrated that the primary analysis results were not sensitive to these departures from normality. To address the potential effect of functional unblinding due to ARIA, the applicant compared the results of the primary analysis using the FAS+ dataset to results using a reduced dataset in which all assessments after occurrence of ARIA (ARIA-E or ARIA-H) were excluded. The results do not suggest a systematic bias due to functional unblinding. Similar results were obtained in an analysis excluding assessments after incidence of an infusion reaction. It is important to reiterate that steps were taken in the protocol to minimize functional blinding, specifically the use of an independent rater who was blinded to patient management, including occurrence of ARIA and dose modifications. Also, ARIA and infusion reactions occurred in the placebo arm, suggesting that investigators could not, with complete accuracy, know the patient's treatment group based on occurrence of an ARIA event or infusion reaction.

Table 7: Study 301 Primary Endpoint Analysis (Sensitivity Analyses)

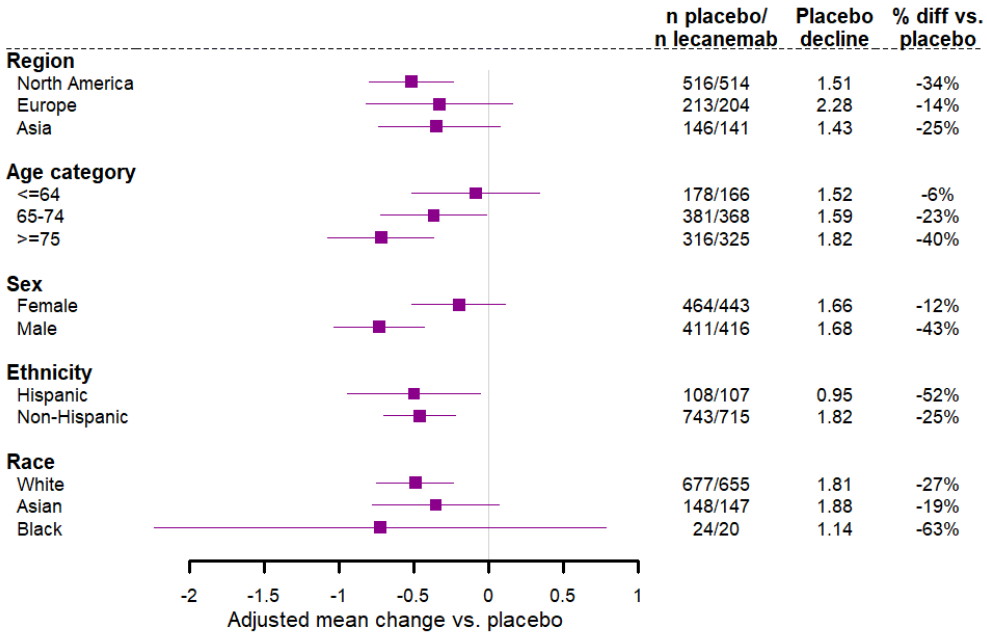
	Per Protocol Population		**Log-Transformation**		**Excluding Assessments After Occurrence of ARIA**	
	Difference vs. Placebo at Week 79 (% difference) p-value		Difference vs. Placebo at Week 79 (% difference) p-value		Difference vs. Placebo at Week 79 (% difference) p-value	
	Placebo Decline (N=799)	**Lecanemab (N=730)**	**Placebo Decline (N=875)**	**Lecanemab (N=859)**	**Placebo Decline (N=875)**	**Lecanemab (N=859)**
CDR-SB	n=695	n=614	n=757	n=714	n=686	n=564
	1.578	-0.436	1.456	-0.416	1.675	-0.524
		-28%		-29%		-31%
		0.00010		0.00002		<0.00001

Source: Tables 14.2.1.2.4, 14.2.1.2.11. and 14.2.1.2.12 from Study 301 CSR

Subgroup Analysis of the Primary Efficacy Endpoint

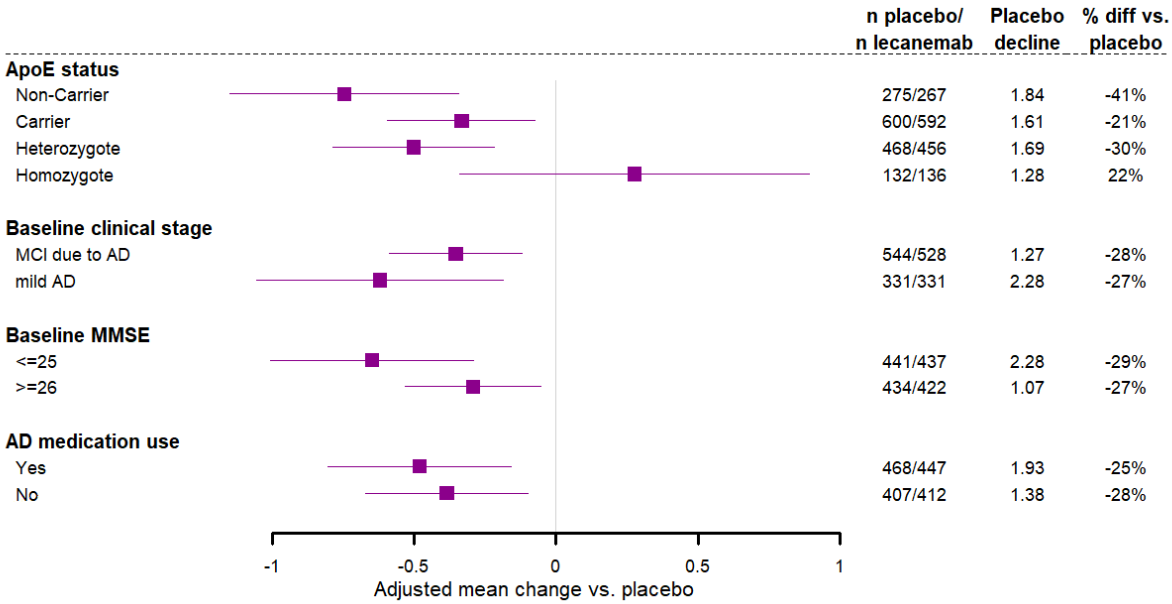
Results of subgroup analyses for the groups described in Section 6.1.1 are provided in Figure 2 and Figure 3. With the notable exception of homozygous ApoE ε4 carriers, all subgroups favored the lecanemab treatment arm compared to placebo. The finding in homozygous ApoE ε4 carriers is discussed in more detail later in this section.

Figure 2: Subgroup Analysis of the Primary Endpoint (Demographics)



Created by the reviewer using Table 14.2.1.1.2 in Study 301 CSR

Figure 3: Subgroup Analysis of the Primary Endpoint (Disease Characteristics)



Created by the reviewer using Table 14.2.1.1.2 in Study 301 CSR

Data Quality and Integrity

There were no major data quality issues identified during the review of Study 301.

Efficacy Results – Secondary clinical endpoints

Statistically significant differences from placebo were observed in the lecanemab treatment arm for all multiplicity-controlled secondary endpoints.

ADAS-Cog 14

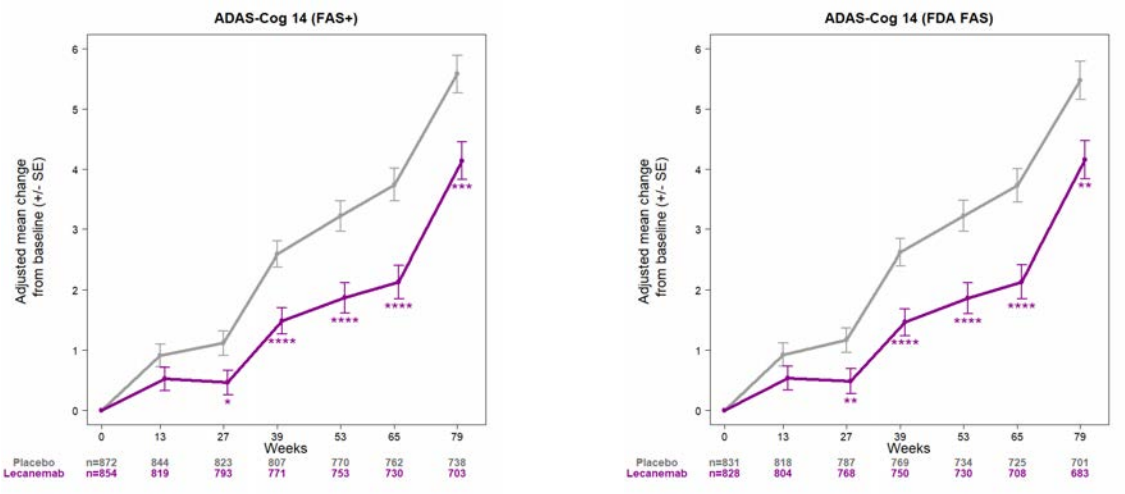
Lecanemab treatment demonstrated a statistically significant reduction in decline on change from baseline ADAS-Cog 14 compared to placebo in the FAS+ population (-1.442 [-26%], p=0.00065) and the FDA FAS population (-1.317 [-24%], p=0.00210) (Table 8). Nominal statistical significance was reached by Week 27 and maintained through Week 79 (Figure 4).

Table 8: Study 301 Secondary Endpoint Analysis (ADAS-Cog 14)

	FAS+		FDA FAS	
	Placebo (N=875)	**Lecanemab** (N=859)	**Placebo** (N=833)	**Lecanemab** (N=833)
Baseline ADAS-Cog 14				
N	873	856	831	830
Mean	24.37	24.45	24.28	24.30
Change from Baseline in ADAS-Cog 14 at Week 79				
n	738	703	701	683
Adjusted mean	5.581	4.140	5.477	4.160
Standard error	0.309	0.314	0.315	0.317
Difference from placebo		-1.442		-1.317
95% CI for difference		(-2.270, -0.613)		(-2.156, -0.479)
% difference vs. placebo		-26%		-24%
p-value (compared with placebo)		0.00065		0.00210

Source: Tables 14.2.2.2.1, 14.2.2.2.2, 14.2.2.2.5, and 14.2.2.2.6 from Study 301 CSR

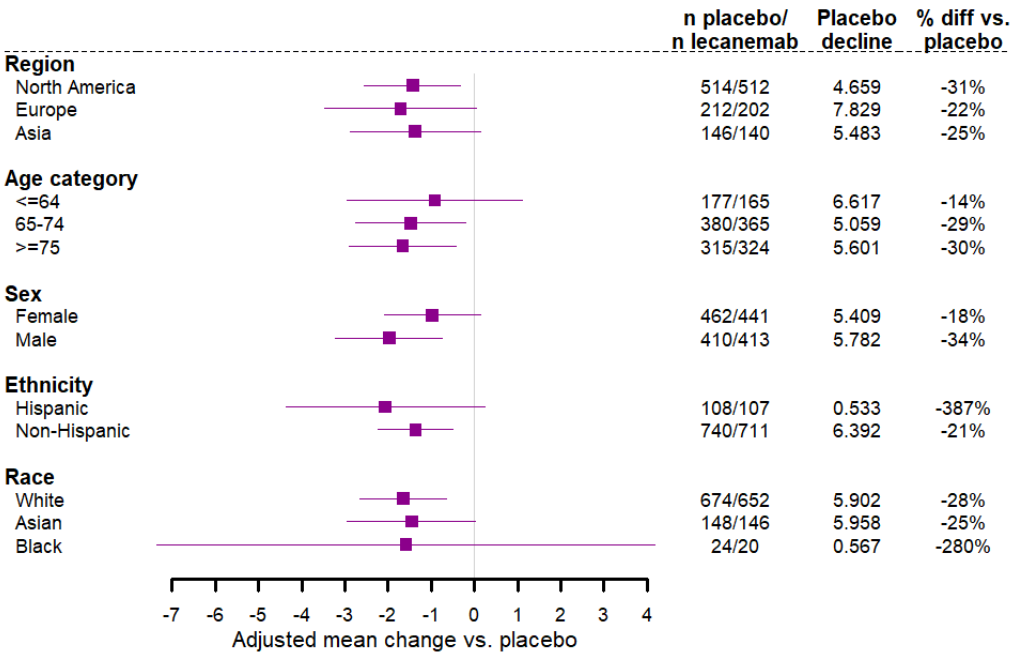
Figure 4: Study 301 Longitudinal Change from Baseline for ADAS-Cog 14 (left – FAS+, right – FDA FAS)



Created by the reviewer
Source: Tables 14.2.2.2.1, 14.2.2.2.2, 14.2.2.2.5, and 14.2.2.2.6 from Study 301 CSR
*p<0.05, **p<0.01, ***p<0.001. ****p<0.0001

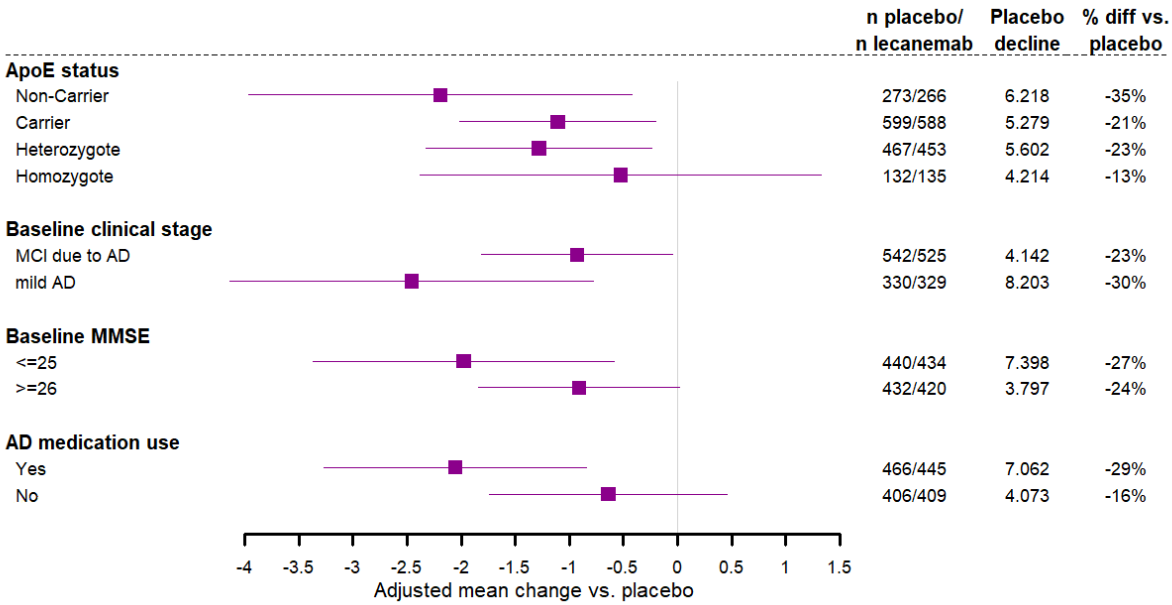
The estimate of the treatment effect favored lecanemab across all prespecified subgroups of interest (Figure 5 and Figure 6).

Figure 5: Subgroup Analysis of ADAS-Cog 14 (Demographics)



Created by the reviewer using Table 14.2.2.2.2 in Study 301 CSR

Figure 6: Subgroup Analysis of ADAS-Cog 14 (Disease Characteristics)



Created by the reviewer using Table 14.2.2.2.2 in Study 301 CSR

ADCOMS

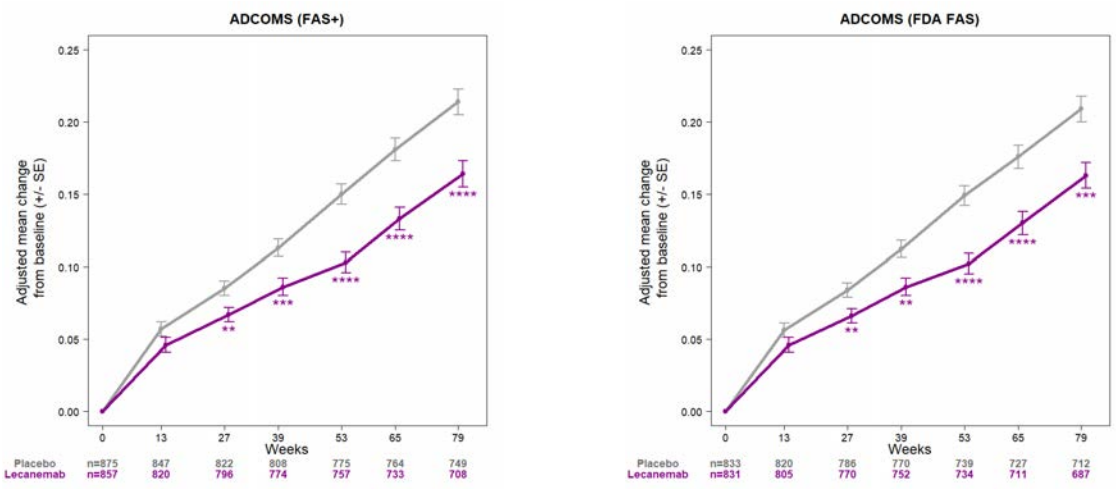
Lecanemab treatment demonstrated a statistically significant reduction in decline on change from baseline ADCOMS compared to placebo in the FAS+ population (-0.050 [-24%], p=0.00002) and the FDA FAS population (-0.045 [-22%], p=0.00017) (Table 9). Nominal statistical significance was reached by Week 27 and maintained through Week 79 (Figure 7).

Table 9: Study 301 Secondary Endpoint Analysis (ADCOMS)

	FAS+		FDA FAS	
	Placebo (N=875)	**Lecanemab** (N=859)	**Placebo** (N=833)	**Lecanemab** (N=833)
Baseline ADCOMS				
N	875	859	833	833
Mean	0.400	0.398	0.399	0.397
Change from Baseline in ADCOMS at Week 79				
n	749	708	712	687
Adjusted mean	0.214	0.164	0.209	0.163
Standard error	0.009	0.009	0.009	0.009
Difference from placebo		-0.050		-0.045
95% CI for difference		(-0.074, -0.027)		(-0.069, -0.022)
% difference vs. placebo		-24%		-22%
p-value (compared with placebo)		0.00002		0.00017

Source: Tables 14.2.2.3.1, 14.2.2.3.2, 14.2.2.3.5, and 14.2.2.3.6 from Study 301 CSR

Figure 7: Study 301 Longitudinal Change from Baseline for ADCOMS (left – FAS+, right – FDA FAS)



Created by the reviewer
Source: Tables 14.2.2.3.1, 14.2.2.3.2, 14.2.2.3.5, and 14.2.2.3.6 from Study 301 CSR
*p<0.05, **p<0.01, ***p<0.001. ****p<0.0001

ADCS-ADL-MCI

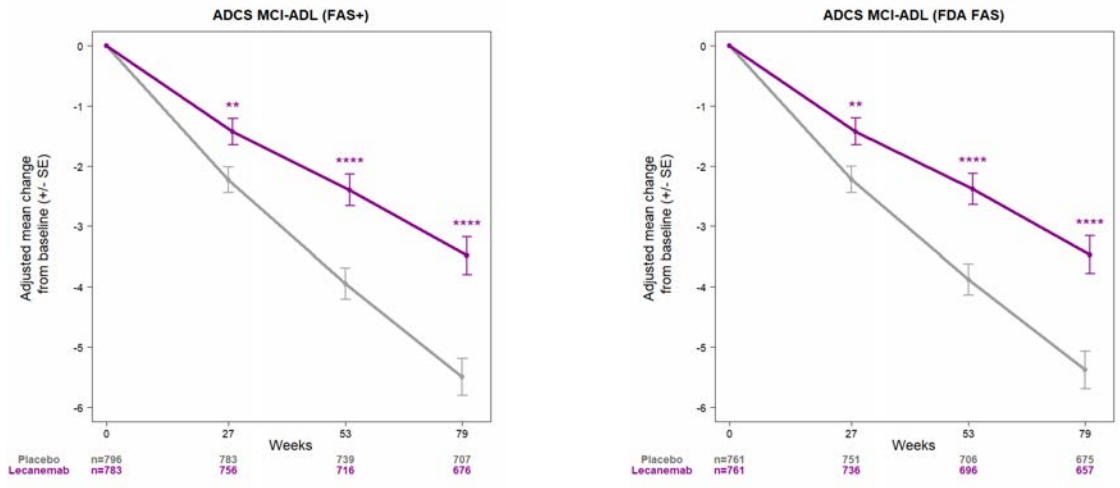
Lecanemab treatment demonstrated a statistically significant reduction in decline on change from baseline ADCS-ADL-MCI compared to placebo in the FAS+ population (2.016 [-37%], p<0.00001) and the FDA FAS population (1.911 [-36%], p<0.00001) (Table 10). Nominal statistical significance was reached by the first post-baseline measurement time of Week 27 and maintained through Week 79 (Figure 8).

Table 10: Study 301 Secondary Endpoint Analysis (ADCS ADL-MCI)

	FAS+		FDA FAS	
	Placebo (N=875)	**Lecanemab** (N=859)	**Placebo** (N=833)	**Lecanemab** (N=833)
Baseline ADCS ADL-MCI				
N	822	808	786	786
Mean	40.9	41.2	41.0	41.2
Change from Baseline in ADCS ADL-MCI at Week 79				
n	707	676	675	657
Adjusted mean	-5.500	-3.484	-5.379	-3.468
Standard error	0.308	0.313	0.313	0.316
Difference from placebo		2.016		1.911
95% CI for difference		(1.208, 2.823)		(1.093, 2.728)
% difference vs. placebo		-37%		-36%
p-value (compared with placebo)		<0.00001		<0.00001

Source: Tables 14.2.2.4.1, 14.2.2.4.2, 14.2.2.4.5, and 14.2.2.4.6 from Study 301 CSR

Figure 8: Study 301 Longitudinal Change from Baseline for ADCS ADL-MCI (left – FAS+, right – FDA FAS)

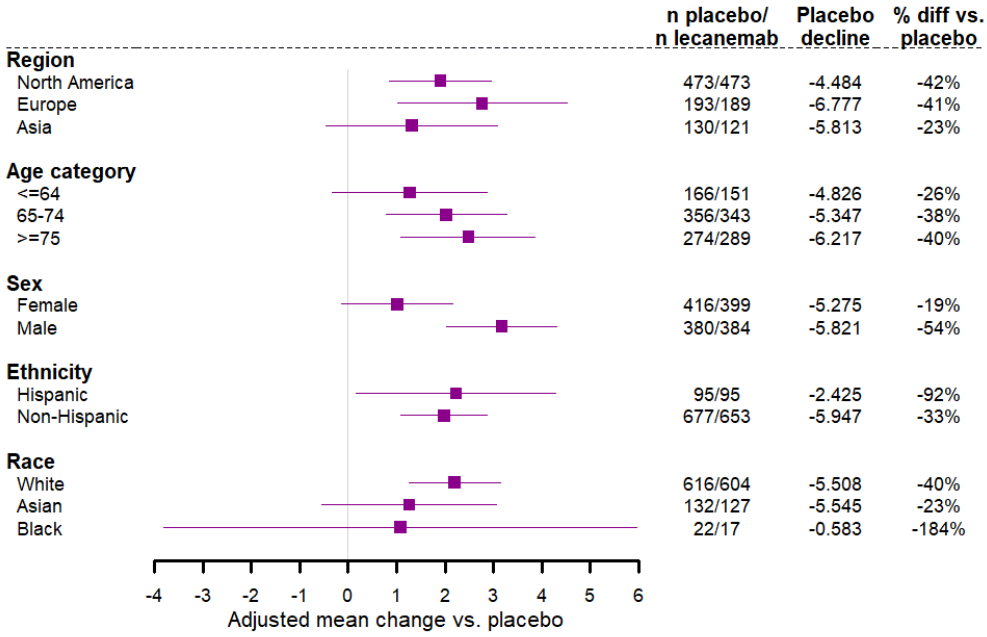


Created by the reviewer
Source: Tables 14.2.2.4.1, 14.2.2.4.2, 14.2.2.4.5, and 14.2.2.4.6 from Study 301 CSR
*p<0.05, **p<0.01, ***p<0.001. ****p<0.0001

Reviewer Comment: ADCS-ADL-MCI assessments were not performed in 111 patients because ADCS-ADL-MCI was originally an exploratory endpoint in the study and there was a delay in implementing the assessment at study sites. The overall interpretation of the results on this endpoint is not meaningfully affected by this missing data.

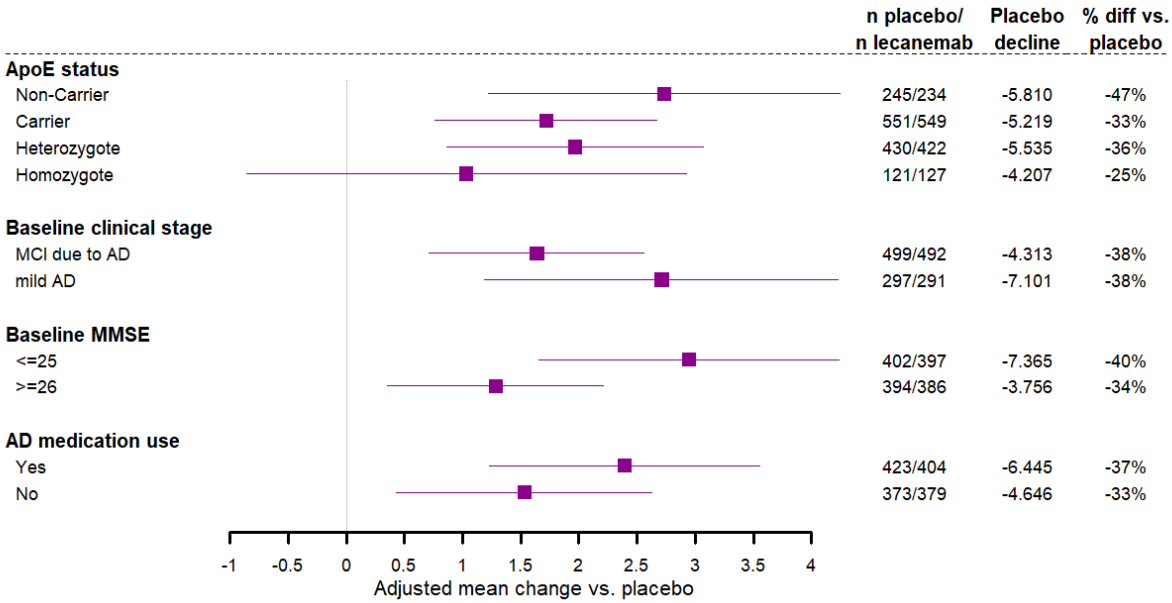
The estimate of the treatment effect favored lecanemab across all prespecified subgroups of interest (Figure 9 and Figure 10).

Figure 9: Subgroup Analysis of ADCS ADL-MCI (Demographics)



Created by the reviewer using Table 14.2.2.4.2 in Study 301 CSR

Figure 10: Subgroup Analysis of ADCS ADL-MCI (Disease Characteristics)



Created by the reviewer using Table 14.2.2.4.2 in Study 301 CSR

Efficacy Results – Pharmacodynamic endpoints

Amyloid PET

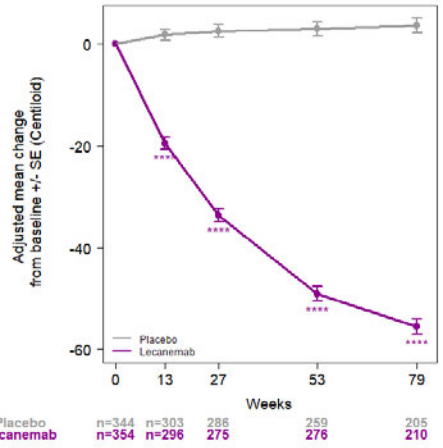
Lecanemab treatment demonstrated a statistically significant treatment effect on change from baseline in brain amyloid as measured by PET and reported as Centiloids at Week 79 (-59.1, p<0.00001) (Table 11). The results indicate a time-dependent relationship (Figure 11). The median [25^{th} – 75^{th} percentile] Centiloid value in lecanemab treated patients at Week 79 was 16.5 [3.8 – 37.3].

Table 11: Study 301 Pharmacodynamic Endpoint Analysis (Amyloid PET)

	Placebo (N=353)	**Lecanemab** (N=363)
Baseline Centiloid		
N	351	360
Mean	75.0	77.9
Change from Baseline in Centiloid at Week 79		
n	205	210
Adjusted mean	3.64	-55.5
Standard error	1.47	1.46
Difference from placebo		-59.1
95% CI for difference		(-62.6, -55.6)
p-value (compared with placebo)		<0.00001

Source: Tables 14.2.2.1.1, and 14.2.2.1.2 from Study 301 CSR

Figure 11: Study 301 Change from Baseline in Brain Amyloid (Centiloid)



Created by the reviewer from Tables 14.2.2.1.1, and 14.2.2.1.2 in Study 301 CSR
****p<0.0001

Tau PET

Regional analyses of tau PET suggested a smaller change from baseline in the lecanemab treatment arm compared to placebo with nominal statistical significance achieved for the temporal, medial temporal, and meta-temporal regions (Table 12). Global tau load computed from the Tau IQ algorithm showed no statistically significant treatment difference -0.005 (-0.017, 0.007], p=0.38.

Table 12: Summary of Tau PET Regional Analysis (Week 79)

	Baseline SUVR		LS Mean Change From Baseline		
Region	Lecanemab (N=135)	Placebo (N=122)	Lecanemab (N=103)	Placebo (N=107)	Difference From Placebo (95% CI)
Whole cortical gray matter	1.427	1.287	0.052	0.087	-0.035 (-0.076, 0.007)
Meta-temporal	1.728	1.609	0.073	0.145	-0.071 (-0.127, -0.016)
Frontal	1.224	1.090	0.030	0.053	-0.023 (-0.060, 0.014)
Cingulate	1.204	1.112	0.023	0.057	-0.034 (-0.078, 0.010)
Parietal	1.481	1.293	0.042	0.071	-0.029 (-0.078, 0.020)
Occipital	1.548	1.393	0.094	0.097	-0.003 (-0.049, 0.044)
Medial temporal	1.562	1.536	0.018	0.086	-0.068 (-0.111, -0.024)
Temporal	1.651	1.521	0.079	0.144	-0.065 (-0.119, -0.012)

Source: Table 14.2.7.2.1 and 14.2.7.2.2 from Study 301 CSR

vMRI

Lecanemab treatment was associated with a decrease in whole brain volume and cortical thickness and an increase in ventricular volume at Week 79 (Table 13). Given the favorable results on clinical endpoints observed in Study 301, the clinical relevance of these changes is unclear. Fluid biomarkers of neurodegeneration, including plasma NfL in Study 301, do not suggest a greater extent of neurodegeneration with lecanemab treatment. It will be important to collect longer-term data in a larger number of patients to further understand the clinical implications, if any, of these observations. It is also important to note that in contrast to the whole brain and ventricular volume changes, lecanemab treatment was associated with a reduction in volume loss in the total hippocampal volume (Table 13).

At an individual level, change from baseline in whole brain volume (decrease) or ventricular volume (increase) is correlated with decline in clinical endpoints in the placebo arm of the study. A similar correlation can therefore be expected to be observed in the lecanemab treatment arm and more likely reflects the underlying disease progression than a drug-induced worsening of decline.

Table 13: Summary of vMRI Analysis (Week 79)

	Baseline (mm^3)		LS Mean Change From Baseline (Week 79)		
Region	Lecanemab (N=805)	Placebo (N=825)	Lecanemab (N=643)	Placebo (N=667)	Difference From Placebo (95% CI)
Hippocampal	6594	6681	-189	-208	19 (6, 32)
Left hippocampal	3230	3279	-95	-106	11 (4, 19)
Right hippocampal	3364	3402	-95	-102	7 (-0.6, 15)
Whole brain	999663	1009173	-21819	-17742	-4077 (-5123, -3030)
Lateral ventricular	44193	43521	7302	5521	1781 (1397, 2164)
Cortical thickness*	2.601	2.608	-0.134	-0.116	-0.018(-0.025, -0.012)

* Cortical thickness is measures in mm
Source: Tables 14.2.7.5.1 and 14.2.7.5.2 from Study 301 CSR

Plasma Biomarkers

Lecanemab treatment was associated with an increase in plasma $A\beta_{42/40}$ and a decrease in plasma p-tau 181 and plasma GFAP compared to placebo at Week 77. There was also a trend of less increase in plasma NfL in the lecanemab treatment arm compared to placebo (Table 14).

Table 14: Summary of Plasma Biomarker Analyses (Week 77)

Biomarker	Baseline		LS Mean Change from Baseline (Week 77)		Difference from Placebo (95% CI)
	Lecanemab	Placebo	Lecanemab	Placebo	
$A\beta_{42/40}$	n=814	n=811	n=648	n=668	0.007
	0.088	0.088	0.008	0.001	(0.006, 0.008)
p-tau 181 (pg/mL)	n=766	n=763	n=590	n=609	-0.776
	3.696	3.740	-0.575	0.201	(-0.904, -0.648)
GFAP (pg/mL)	n=759	n=745	n=560	n=552	-84.0
	355.6	361.1	-47.1	36.9	(-101.5, -66.4)
NfL (pg/mL)	n=728	n=746	n=529	n=574	-1.1
	21.9	22.2	1.8	2.9	(-2.3, 0.11)

Source: Tables 14.2.7.3.1 and 14.2.7.3.2 from Study 301 CSR

CSF Biomarkers

Lecanemab treatment was associated with an increase in CSF $A\beta_{1-42}$ and a decrease in p-tau 181, t-tau, and neurogranin as compared to placebo at Week 77. Trends for less decrease in $A\beta_{1-40}$ and less increase in NfL in the lecanemab treatment arm compared to placebo were also observed (Table 15).

Table 15: Summary of CSF Biomarker Analyses (Week 77)

Biomarker	Baseline		LS Mean Change from Baseline (Week 77)		Difference from Placebo (95% CI)
	Lecanemab	Placebo	Lecanemab	Placebo	
$A\beta_{1-42}$ (pg/mL)	n=142	n=137	n=101	n=97	289.8
	547.0	514.4	287.3	-2.5	(238.5, 341.1)
$A\beta_{1-40}$ (pg/mL)	n=112	n=110	n=71	n=71	-352.3
	11987	12334	-439.8	-87.5	(-1057.4, 352.8)
t-tau (pg/mL)	n=142	n=139	n=101	n=98	-124.9
	585	615	-30.4	94.5	(-169.1, -80.8)
p-tau 181 (pg/mL)	n=142	n=139	n=101	n=98	-28.5
	84.9	92.1	-16.1	12.4	(-34.5, -22.5)
neurogranin (pg/mL)	n=139	n=134	n=104	n=97	-89.7
	500	519	-71.4	18.3	(-128.3, -51.1)
NfL (pg/mL)	n=139	n=134	n=104	n=97	-26.7
	1201	1110	51.6	78.4	(-168.9, 115.4)

Source: Tables 14.2.7.4.1 and 14.2.7.4.2 from Study 301 CSR

Efficacy Results – Health-Related Quality of Life Assessments

Lecanemab treatment was associated with a reduction in decline in the EQ-5D-5L Health Today score by subject and QOL-AD total score by subject and care partner as proxy, and a reduction in the increase of the Zarit Burden Interview total score at Week 79 compared to placebo (Table

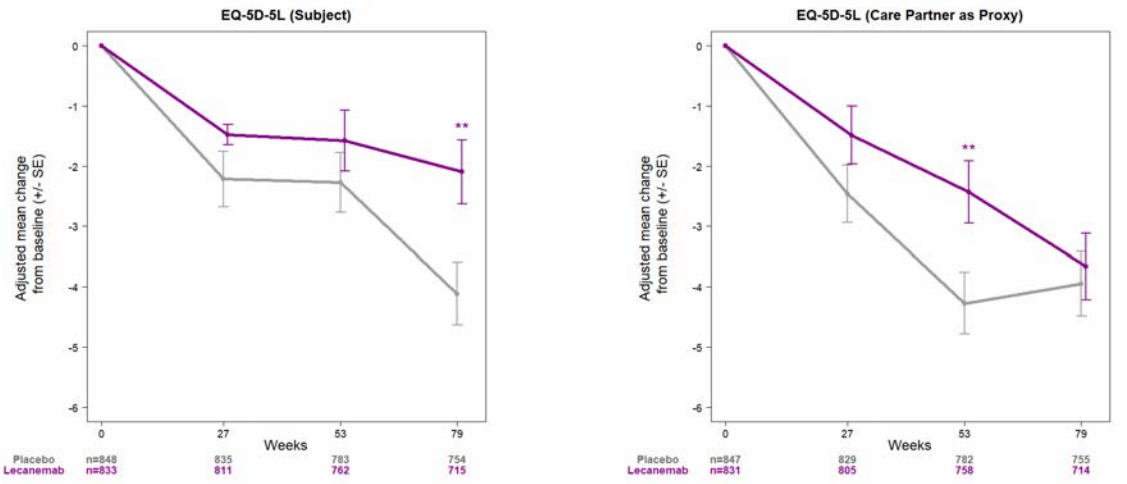
16). No treatment effect was observed for the EQ-5D-5L by care partner or by care partner as proxy. The longitudinal changes from baseline for health-related quality of life assessments are illustrated in Figure 12.

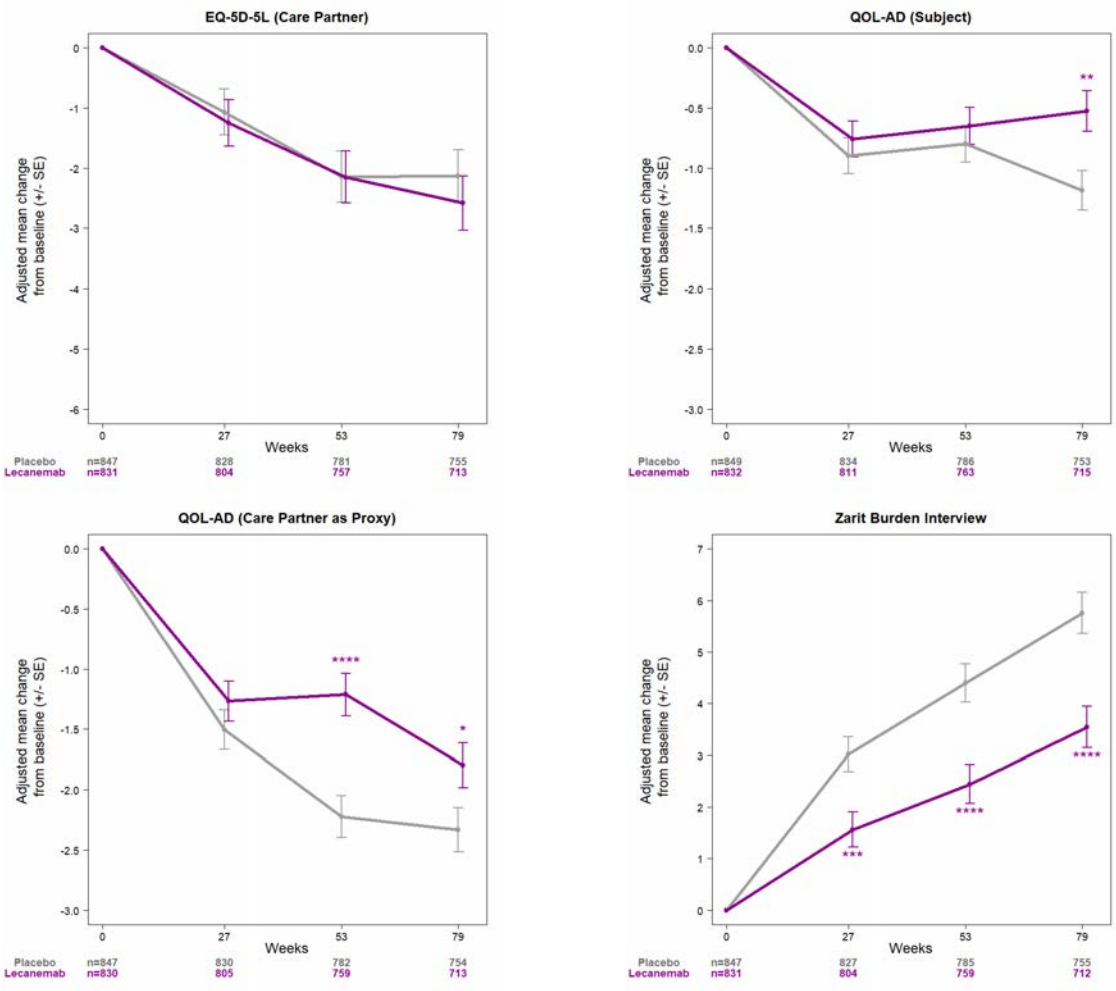
Table 16: Study 301 Health-Related Quality of Life Assessment Analysis (FAS+, Week 79)

	Placebo Decline (N=875)		Lecanemab (N=859)		
Health-Related Quality of Life Assessment	**n**	**Adjusted Mean**	**n**	**Difference vs. Placebo (%)**	**(95% CI)**
EQ-5D-5L (subject): Health Today	754	-4.1	715	2.0 (-49%)	(0.65, 3.4)
EQ-5D-5L (care partner as proxy): Health Today	755	-3.9	714	0.29 (-7%)	(-1.1, 1.7)
EQ-5D-5L (care partner): Health Today	755	-2.1	713	-0.45 (21%)	(-1.6, 0.70)
QOL-AD (subject)	753	-1.2	715	0.66 (-56%)	(0.24, 1.1)
QOL-AD (care partner as proxy)	754	-2.3	713	0.54 (-23%)	(0.07, 1.0)
Zarit Burden Interview	755	5.8	712	-2.2 (-38%)	(-3.2, -1.2)

Source: Tables 14.2.3.4.1, 14.2.3.4.2, 14.2.3.5.1, 14.2.3.5.2, 14.2.3.6.1, and 14.2.3.6.2 from Study 301 CSR

Figure 12: Study 301 Longitudinal Change from Baseline for Health-Related Quality of Life Assessments





Created by the reviewer
Source: Tables 14.2.3.4.1, 14.2.3.4.2, 14.2.3.5.1, 14.2.3.5.2, 14.2.3.6.1, and 14.2.3.6.2 from Study 301 CSR
*p<0.05, **p<0.01, ***p<0.001. ****p<0.0001

Dose/Dose Response

Dose-response was addressed in the original review for accelerated approval (Krudys, DARRTS 1/05/2023).

Durability of Response

Statistically significant treatment effects for the primary and all secondary endpoints were observed by the 6-month visit. In general, the absolute treatment difference for the primary and secondary endpoints tended to increase over time for the 18 months of the placebo-controlled portion of the study. Amyloid plaque continued to decline to levels consistent with

amyloid negativity following dosing with lecanemab 10 mg/kg biweekly. It is anticipated that with a drug that impacts underlying disease biology that the treatment benefit will increase over time and that is, in fact, what is demonstrated in Study 301.

Persistence of Effect

Lecanemab treatment in this study was intended to be continuous. Treatment may have been stopped or withheld for reasons of safety, but this data is insufficient to draw conclusions regarding persistence of effect. The gap period from Study 201 suggested that the treatment difference observed in the double-blind portion of the study was maintained after the approximately two year off-treatment period.

Subpopulations

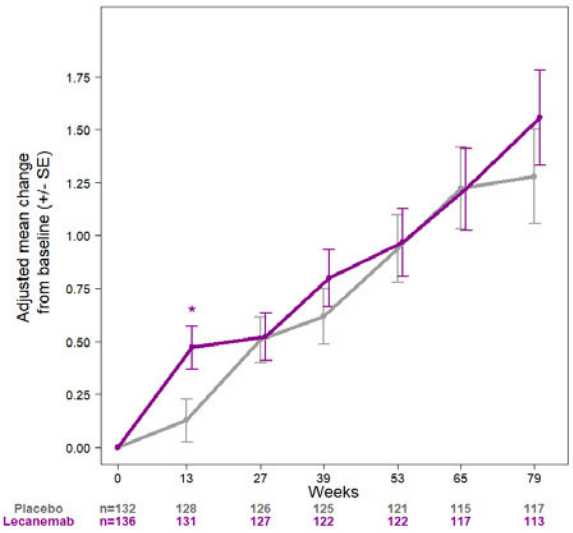
Results favoring lecanemab were observed for the primary and secondary endpoints across subgroups of interest defined by demographic and baseline disease characteristics (Figure 2, Figure 3, Figure 5, Figure 6, Figure 9, and Figure 10). The homozygous ApoE ε4 carrier subgroup deserves further attention because of 1) the increased risk of ARIA in this subpopulation and 2) the apparent lack of treatment effect on CDR-SB in this population (Figure 3).

Before reviewing the data from Study 301 it is important to consider prior expectations regarding efficacy in homozygous ApoE ε4 carriers. In the briefing document for the December 17, 2021 Type B Meeting, the applicant postulated that the magnitude of the effect would be greater for the ApoE ε4 carrier population based on the mechanism of action of lecanemab and the fact that increased levels of soluble amyloid aggregate species have been observed in ApoE ε4 carrier pathological specimens compared to non-carriers. Study 201 was too small for meaningful subgroup analysis, but there appeared to be a trend for a greater magnitude of effect in the ApoE ε4 carrier subgroup (Massie, DARRTS 12/19/2022). Although there have been inconsistent findings in ApoE ε4 carrier subgroups across studies, the generally accepted view has been that ApoE ε4 carriers should have the same or better response that non-carriers to amyloid-targeting therapies (Evans et al. 2023).

Trial design and execution of Study 301 are also relevant considerations for interpretation of efficacy in subgroups. Randomization was stratified based on ApoE ε4 status (carrier/non-carrier) and not genotype (heterozygous/homozygous). ApoE ε4 genotype was one of 9 subgroups specified in the analysis plan and should be considered exploratory. The size of the homozygous ApoE ε4 carrier population (16%) was also one of the smallest subgroups tested in the study and is reflected in the wide confidence intervals associated with estimates of treatment effect. The ICH E9 Guidance states that, “when exploratory, these analyses should be interpreted cautiously; any conclusion of treatment efficacy (or lack thereof) or safety based solely on exploratory subgroup analyses are unlikely to be accepted.”

Notwithstanding these considerations, the estimate of the treatment effect on CDR-SB at Week 79 was 0.28 in favor of placebo (22% worsening with lecanemab treatment) in the homozygous ApoE ε4 carrier subgroup, which could be a concerning observation when viewed in isolation. The longitudinal results in this subpopulation, however, show that the change from baseline in CDR-SB was largely overlapping for the treatment and placebo arms from Week 27 onward, with the exception of an unanticipated flattening of the placebo curve between Weeks 65 and 79 (Figure 13). These results are inconsistent with a systematic worsening with lecanemab treatment in this subgroup.

Figure 13: Primary Endpoint Analysis (FAS+) in Homozygous ApoE ε4 Subgroup



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Source: Table 14.2.1.1.2 in Study 301 CSR
*p<0.05,

Results for the key secondary endpoints of ADAS-Cog 14 and ADCS-ADL-MCI favor lecanemab in the homozygous ApoE ε4 carrier subgroup, with point estimates reflecting 13% and 25% reduction in clinical decline, respectively (Figure 6 and Figure 10). Discordant results between CDR-SB and ADAS-Cog 14 and ADCS-ADL-MCI have been observed in other studies. Similarly, results for health-related quality of life assessments in homozygous ApoE ε4 carriers are consistent with the overall results and support a treatment effect (Figure 14).

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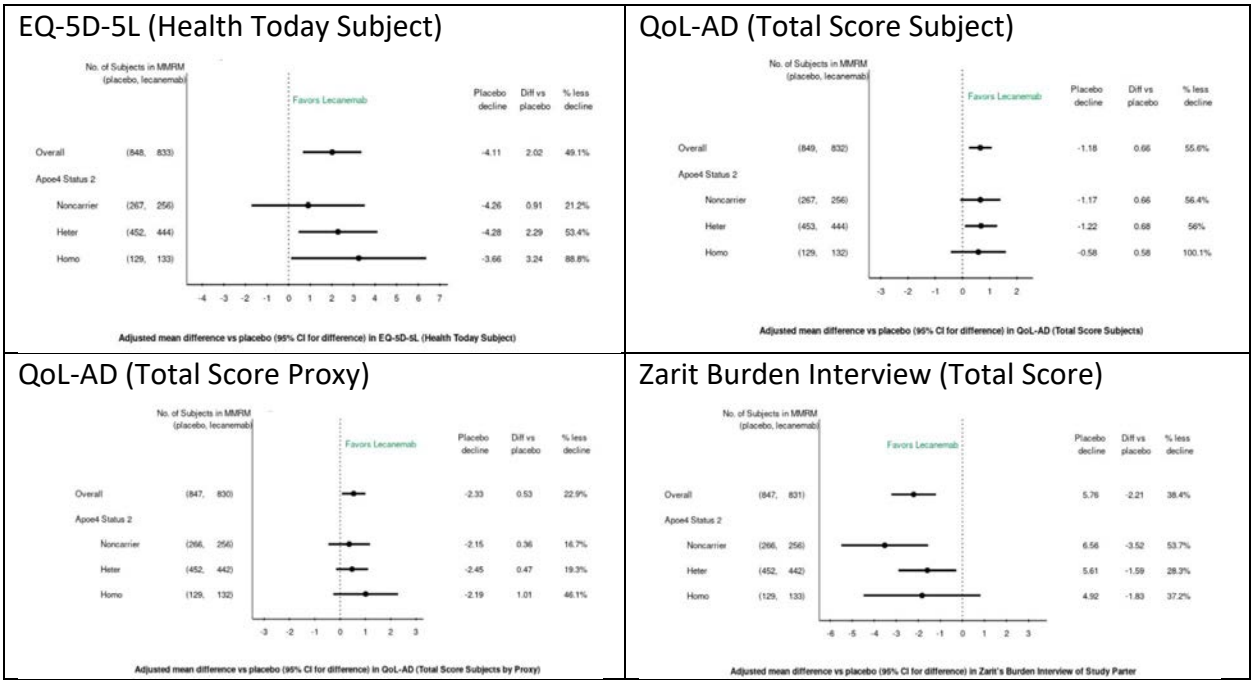
Figure 14: Health-Related Quality of Life Assessment Analysis by ApoE ε4 Carrier Status



Source: Figure 17 in Clinical Overview

Importantly, consistent effects on biomarkers were observed in homozygous ApoE ε4 carriers (see clinical pharmacology review), suggesting that the underlying pharmacology and drug action is preserved in this population. Together, these results support a treatment effect in homozygous ApoE ε4 carriers, but there remains uncertainty regarding the magnitude of the treatment effect and how it compares to the magnitude of the treatment effect in heterozygous ApoE ε4 carriers and non-carriers.

Additional Analyses Conducted on the Individual Trial

Planned exploratory analyses were conducted by the applicant and provide additional context for the positive results on the primary and secondary endpoints.

The modified integrated Alzheimer's Disease Rating Scale (iADRS) is a simple linear combination of the ADAS-Cog 14 and the ADCS-ADL-MCI and is purported to be more sensitive to change and treatment effects in patients at the early stages of the disease. Lecanemab treatment demonstrated a statistically significant reduction in decline on change from baseline the modified iADRS compared to placebo in the FAS+ population (3.157 [-30%], p=0.00001) (Table 17).

Table 17: Study 301 Exploratory Endpoint Analysis of modified iADRS (FAS+, Week 79)

	Placebo (N=875)	Lecanemab (N=859)
Baseline modified iADRS		
N	820	806
Mean	106.5	106.9
Change from Baseline in modified iADRS at Week 79		
n	689	662
Adjusted mean	-10.5	-7.3
Standard error	0.54	0.55
Difference from placebo		3.2
95% CI for difference		(1.7, 4.6)
% difference vs. placebo		-30%
p-value (compared with placebo)		0.00001

Source: Tables 14.2.3.1.1, and 14.2.3.1.2 from Study 301 CSR

Time to worsening of the global CDR score, defined as time from randomization to first increase from baseline by at least 0.5 points in two consecutive visits, was analyzed using Cox regression adjusting for stratification variables. Lecanemab treatment reduced the risk of progression on the CDR global score by 31% with a hazard ratio of 0.69 (0.572, 0.833), p=0.00011.

7. Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

This section is not applicable to this review because only one trial is reviewed.

7.2. Additional Efficacy Considerations

7.2.1. Considerations on Benefit in the Postmarket Setting

The population enrolled in Study 301 did not include patients at either end of the Alzheimer's disease continuum and there is some uncertainty with respect to the generalizability of benefit across the entire spectrum of Alzheimer's disease. There is a general expectation, however, that initiating treatment with lecanemab earlier in the disease may provide the best opportunity to delay or halt the pathophysiological processes that lead to the clinical deficits of Alzheimer's disease. The ongoing study (Study 303) of lecanemab in individuals in Stages 1 and 2 of Alzheimer's disease should shed light on potential benefit in this population. Intervention with lecanemab later in the disease may be expected to provide less benefit, as downstream pathological processes may dominate.

Individuals with Down syndrome represent another important population at risk for Alzheimer's disease who might also benefit from treatment with lecanemab. Alzheimer's disease in individuals with Down syndrome is likely driven by an overexpression of the gene for amyloid precursor protein located on chromosome 21, thus the pathology in this population is similar to that found in dominantly inherited Alzheimer's disease and sporadic Alzheimer's disease. One challenge is assessing changes in cognition and function in a population with intellectual disability. Also, individuals with Down syndrome have a higher incidence of cerebral amyloid angiopathy. Therefore, additional safety data would be helpful to inform risk-benefit considerations in this population.

7.3. Integrated Assessment of Effectiveness

Lecanemab received accelerated approval based on data from Study 201 that demonstrated substantial evidence of effectiveness on a reasonably likely surrogate endpoint, reduction in brain amyloid beta plaques as measured by PET imaging. The results of Study 301 verify and describe the clinical benefit of lecanemab for the treatment of Alzheimer's disease. The collective evidence from Study 201 and 301 continue to demonstrate substantial evidence of effectiveness for lecanemab for the treatment of Alzheimer's disease, and support the traditional approval of lecanemab in this population.

The effect on the primary endpoint in Study 301 is persuasive and reinforced by statistically significant results for all 4 multiplicity-controlled secondary endpoints, including endpoints capturing distinct information regarding cognitive decline. The treatment effect was apparent by the 6-month visit and the absolute treatment difference tended to increase with time. The robustness of the observed treatment effect was demonstrated by sensitivity analyses, including those assessing the impact of non-normality and the potential for functional unblinding. The treatment effect in Study 301 is supported by the consistently favorable results for the primary and secondary endpoints across subgroups of interest defined by demographic and baseline disease characteristics. Biomarkers reflecting target engagement, effects on downstream tau pathophysiology, and neurodegeneration support the observations on the clinical endpoints.

The effect on the primary endpoint, CDR-SB, represents a clinically meaningful reduction of clinical decline. CDR-SB is an integrated scale that meaningfully assesses both daily function and cognitive effects. Any increment of change on an individual domain of the CDR-SB (e.g., a change of 0.5 or 1) is clinically meaningful for an individual patient. Therefore, a group-level mean change from baseline on the CDR-SB that is reduced, to a statistically significant extent in an appropriately powered study, compared to placebo may be considered clinically meaningful.

It is useful to interpret treatment difference as a percent reduction rather than the absolute point difference which depends on the length of the study and the disease stage. The results of

study 301 demonstrate a reduced decline of approximately 25% to 40% on clinical endpoints. For the primary endpoint, this corresponds to a preservation of CDR-SB by approximately 5.3 months relative to placebo over the 18 months of the study. This preservation of cognitive function is clearly clinically meaningful. Further context is provided by the exploratory analysis demonstrating a 31% reduction in the risk of progression on the global CDR score and the observed treatment effects on health-related quality of life assessments.

8. Review of Safety

Please see the separate safety review by Dr. Erten-Lyons.

9. Advisory Committee Meeting and Other External Consultations

An advisory committee meeting was held on June 9, 2023, to discuss the data from Study 301 and whether the data verify the clinical benefit of lecanemab for the treatment of AD, and to discuss whether the data impact the established benefit-risk assessment for lecanemab.

There were minor typographical errors in a few of the tables in the FDA Briefing Document. The updated tables are provided in this review (Table 12, Table 13, and Table 16).

The committee discussed whether the data from 301 showed clear and robust evidence of effectiveness. The committee voted unanimously, 6-0, that the data confirm the clinical benefit of lecanemab for the treatment of AD.

The committee then discussed the overall benefit-risk assessment of lecanemab for the treatment of AD. The committee opined that the overall benefit-risk assessment for the population of patients with AD who were enrolled in Study 301 appeared favorable and supported traditional approval.

The panel discussion then focused on the following specific patient subgroups that the Agency had identified in the briefing document and discussion question as being more challenging in assessing benefit-risk.

- Apolipoprotein E (ApoE) ε4 homozygotes
- Patients requiring concomitant treatment with anticoagulant agents
- Patients with cerebral amyloid angiopathy

<u>Apolipoprotein E (ApoE) ε4 homozygotes</u>

The presence of the ApoE E ε4 allele increases the risk of ARIA, with greater risk observed in homozygotes than heterozygotes. In Study 301, subgroup analyses by ApoE ε4 status by carrier or noncarrier demonstrated a statistically significant treatment effect in both groups; however, a further subgroup analysis of the carriers by heterozygote and homozygote status suggests that there could potentially be lower efficacy in the homozygote subgroup treated with lecanemab; however, there are limitations to the interpretability of this data such as the small size of this subgroup.

The committee indicated that they thought that the drug was still effective in ApoE ε4 homozygotes, noting the consistency across the secondary endpoints and limitations with a small sample size. The consensus appeared to be that the benefit-risk remained favorable for ApoE ε4 homozygotes, although some members questioned if the dosing regimen could be further optimized in this population. The committee also noted that language regarding recommendations for ApoE genotyping to inform risk should be stronger in labeling.

Patients requiring concomitant treatment with anticoagulant agents

In Study 301, baseline use of antithrombotic medication (aspirin, other antiplatelets, or anticoagulants) was allowed if the patient was on a stable dose. The majority of exposures to antithrombotic medications were to aspirin. Antithrombotic medications did not increase the risk of ARIA with LEQEMBI. The incidence of cerebral hemorrhage was 0.9% (3/328 patients) in patients taking LEQEMBI with a concomitant antithrombotic medication at the time of the event compared to 0.6% (3/545 patients) in those who did not receive an antithrombotic. Patients taking LEQEMBI with an anticoagulant alone or combined with an antiplatelet medication or aspirin had an incidence of cerebral hemorrhage of 2.5% (2/79 patients).

Current labeling advises: “Because intracerebral hemorrhages greater than 1 cm in diameter have been observed in patients taking LEQEMBI, additional caution should be exercised when considering the administration of anticoagulants or a thrombolytic agent (e.g., tissue plasminogen activator) to a patient already being treated with LEQEMBI.”

There were split opinions in the panel regarding whether patients should be treated with concomitant anticoagulant medications and lecanemab. However, more panelists favored not excluding patients taking anticoagulant medication from treatment with lecanemab and allowing for prescriber clinical judgement based on individual evaluation.

Patients with cerebral amyloid angiopathy

Risk of ARIA may be greater in patients with underlying cerebral amyloid angiopathy (CAA) or more severe CAA. In the clinical trials with lecanemab, subjects with MRI findings consistent with CAA (i.e., more than 4 microhemorrhages, a single hemorrhage greater than 10mm, an

area of superficial siderosis) were not enrolled; however, there is a high background rate of CAA in AD and many individuals with CAA do not have the characteristic findings on MRI. This makes identification of patients with CAA difficult and limits the ability to make specific recommendations to mitigate any increased risk of ARIA, if CAA does pose an increased risk. There are individuals with identified CAA pathology who have had serious outcomes during treatment with lecanemab; however, given the high background rate of CAA, there are also many individuals who likely have CAA pathology who have received treatment with lecanemab and have not experienced significant adverse events. The current prescribing information does not specifically address the potential risk of lecanemab use with CAA but does list risk factors for intracerebral hemorrhage such as prior cerebral hemorrhage greater than 1 cm in greatest diameter, more than 4 microhemorrhages, superficial siderosis, evidence of vasogenic edema. The prescribing information states that caution should be exercised when considering the use of LEQEMBI in patients with these risk factors.

During the discussion, FDA provided information on the criteria for contraindications, noting that contraindications were typically informed by clinical data, and, in this situation, there is a theoretical risk but little data in patients that were excluded to adequately define the risk. The panel noted that it would be difficult to exclude patients for a condition that does not have definitive clinical diagnostic criteria. However, it was noted that the potential risk with CAA could be more clearly stated in the label which could then help inform prescribers and patients about potential risks.

10. Labeling Recommendations

10.1. Prescription Drug Labeling

Edits to the prescribing information have been proposed, but the labeling has not been finalized at the time of this review.

10.2. Nonprescription Drug Labeling

Not applicable.

11. Risk Evaluation and Mitigation Strategies (REMS)

Please see the separate safety review by Dr. Erten-Lyons for considerations regarding a REMS.

12. Postmarketing Requirements and Commitments

Post-marketing requirements and/or commitments are still under discussion at this time of this review.

13. Appendices

13.1. References

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13.2. **Financial Disclosure**

Covered Clinical Study (Name and/or Number): 301

Was a list of clinical investigators provided:	Yes ☒	No ☐
Total number of investigators identified: >2500		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 13		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: 13 Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐

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/s/

KEVIN M KRUDYS
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CLINICAL REVIEW

Application Type	Supplemental BLA
Application Number(s)	761269 S001
Priority or Standard	Priority
Submit Date(s)	January 6, 2023
Received Date(s)	January 6, 2023
PDUFA Goal Date	July 6, 2023
Division/Office	Division of Neurology 1, Office of Neuroscience
Reviewer Name(s)	Deniz Erten-Lyons, MD
Review Completion Date	July 5, 2023
Established/Proper Name	Lecanemab
(Proposed) Trade Name	LEQEMBI
Applicant	EISAI
Dosage Form(s)	Intravenous infusion
Applicant Proposed Dosing Regimen(s)	10 mg/kg every two weeks (biweekly)
Applicant Proposed Indication(s)/Population(s)	Early Alzheimer's disease
Recommendation on Regulatory Action	If efficacy is demonstrated and the benefits of lecanemab outweigh the risks, then I recommend approval include appropriate labeling language to address adverse reactions of concern.
Recommended Indication(s)/Population(s) (if applicable)	Indicated for the treatment of early Alzheimer's disease, including patients with mild cognitive impairment and mild Alzheimer's dementia

Table of Contents

Glossary

AC	advisory committee
AD	Alzheimer's disease
ADA	Anti-drug antibody
ADAE	adverse event dataset
AE	adverse event
AESI	adverse event of special interest
AR	adverse reaction
ApoE ε4	apolipoprotein ε4 variant
ARIA	amyloid related imaging abnormality
ARIA-E	amyloid related imaging abnormality edema/effusion
ARIA-H	amyloid related imaging abnormality hemorrhage
BIL	bilirubin
BLA	biologics license application
CAA	Cerebral Amyloid Angiopathy
CDER	Center for Drug Evaluation and Research
CFR	Code of Federal Regulations
CIOMS	Council for International Organizations of Medical Sciences
CMC	chemistry, manufacturing, and controls
CORE	double blind placebo controlled period
CRF	case report form
CSR	clinical study report
C-SSRS	Columbia -Suicide Severity Rating Scale
CSS	Controlled Substance Staff
CTCAE	Common Terminology Criteria for Adverse Events
DSMB	data safety monitoring board
ECG	electrocardiogram
eCTD	electronic common technical document
FDA	Food and Drug Administration
FMQ	FDA Medical Query
GCP	good clinical practice
ICH	International Council for Harmonization
IND	Investigational New Drug Application
ISS	integrated summary of safety
IR	information request
ITT	intent to treat
IV	intravenous
LEC	lecanemab
LEC2.5-BW	lecanemab 2.5 mg/kg bi-weekly (once every two weeks)
LEC5-M	lecanemab 5 mg/kg monthly (once a month)

LEC5-BW	lecanemab 5 mg/kg bi-weekly (once every two weeks)
LE10-M	lecanemab 10 mg/kg monthly (once a month)
LEC10-BW	lecanemab 10mg bi-weekly (once every two weeks)
LLN	lower limit of normal
mAB	monoclonal antibody
MAD	multiple ascending dose
MCI	mild cognitive impairment
MAED	MedDRA-Based Adverse Event Diagnostics
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial infarction
MMSE	Mini Mental State Examination
MQG	medical query group
MRI	magnetic Resonance Imaging
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
OBP	Office of Biotechnology Products
OCS	Office of Computational Science
OCP	Office of Clinical Pharmacology
OLE	open label extension phase
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PD	pharmacodynamics
PDUFA	Prescription Drug User Fee Act
PET	positron emission tomography
PI	prescribing information or package insert
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PO	per oral
PP	per protocol
PPI	patient package insert
PT	preferred term
REMS	risk evaluation and mitigation strategy
QD	once daily
sBLA	supplemental BLA
SAD	single ascending dose
SAE	serious adverse event
SAP	statistical analysis plan
SMQ	standardized MedDRA Queries
SOC	system organ class
SUVR	standardized uptake value ratio
TEAE	treatment emergent adverse event

TEMAV	treatment-emergent markedly abnormal laboratory values
TFNE	transient focal neurological episodes
TIA	transient ischemic attack
tPA	tissue plasminogen activator
ULN	upper limit of normal
UTI	urinary tract infection

1. Executive Summary

1.1. Product Introduction

The reader is referred to the review of clinical efficacy by Dr. Kevin Krudys.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The reader is referred to the review of clinical efficacy by Dr. Kevin Krudys.

1.3. Benefit-Risk Assessment

See Summary Memo for Risk Benefit Assessment and Benefit Risk Dimensions

Benefit-Risk Dimensions

1.4. Patient Experience Data

The reader is referred to the review of clinical efficacy by Dr. Kevin Krudys.

2. Therapeutic Context

2.1. Analysis of Condition

The reader is referred to the review of clinical efficacy by Dr. Kevin Krudys.

2.2. Analysis of Current Treatment Options

The reader is referred to the review of clinical efficacy by Dr. Kevin Krudys.

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

The reader is referred to the review of clinical efficacy by Dr. Kevin Krudys.

3.2. Summary of Presubmission/Submission Regulatory Activity

The reader is referred to the review of clinical efficacy by Dr. Kevin Krudys.

3.3. Foreign Regulatory Actions and Marketing History

There is no foreign marketing experience with lecanemab.

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

During the review of the original BLA, the Office of Clinical Pharmacology (OCP) and Office of Biotechnology Products (OBP) determined that the applicant's ADA assay was not reliable for accurate classification of ADA status, due to interference by serum lecanemab concentrations, possibly resulting in an underestimation of the incidence of antibody formation. In the present

submission, the assay remains inadequate. Therefore, a safety review for immunogenicity could not be conducted. Please refer to OCP and OBP reviews for further details.

4.1. Office of Scientific Investigations (OSI)

The reader is referred to the OSI review.

4.2. Product Quality

The reader is referred to the Product Quality review

4.3. Clinical Microbiology

Not applicable.

4.4. Nonclinical Pharmacology/Toxicology

The reader is referred to the Nonclinical Pharmacology review.

4.5. Clinical Pharmacology

The reader is referred to the Clinical Pharmacology review.

4.6. Devices and Companion Diagnostic Issues

Not Applicable.

4.7. Consumer Study Reviews

Not applicable.

5. Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

The reader is referred to the review of clinical efficacy by Dr. Kevin Krudys for a table of clinical studies. For a table of key clinical studies for the safety review, see section 8.1.

5.2. Review Strategy

The clinical review of biologics license application (BLA) 761269-S001 is divided into a review of clinical efficacy (by Dr. Kevin Krudys), and this review of clinical safety. Information submitted as part of BLA 761269-S001, and published literature are discussed in this review. I will primarily present analysis conducted by myself and clinical data analyst Dr. Rui Li. The primary safety review presented here will focus on Study 301 Core (double-blinded, placebo-controlled period) and Study 301 open-label extension (OLE). Study 201 OLE, Study 201 Core, and two phase 1 studies, Study 104 and Study 101, have been reviewed under BLA 761269. New data since the original submission from the ongoing 201 OLE will provide additional supportive safety data, and ongoing studies Study 303 and DIAN-TU -001 will provide supportive blinded safety data.

In order to identify adverse event signals that may be missed when using individual preferred terms, in addition to using standardized MedDRA Queries (SMQs), FDA-created medical query groups (MQGs) were used as part of the adverse event analysis. These FDA-created MQGs were either broad (B) or narrow (N). Narrow FDA-MQG terms identify more specific medical concepts whereas Broad FDA-MQGs cast a wider net than narrow query terms for signal detecting and are less specific.

6. Review of Relevant Individual Trials Used to Support Efficacy

The reader is referred to the review of clinical efficacy by Dr. Kevin Krudys.

7. Review of Safety

7.1. Safety Review Approach

The clinical data submitted to BLA 761269-S001 on January 6, 2023, presented all lecanemab data as of September 13, 2022, for Study 301 Core, and, as of April 15, 2022, for ongoing studies. Additional safety data were provided at the time of the 90-day update, for this priority review, on April 7, 2023, with a data cut off of December 1, 2022.

The phase 3 Study 301 Core and its open-label extension (OLE) phase provide the primary data set for the safety review for this efficacy supplement of lecanemab. Ongoing Study 201 OLE provides supportive safety data. The two ongoing studies, Study 303 (phase 3) and Study Dian-TU (phase 2/3), provide blinded safety information. Additionally, since Study 301 Core in China is also ongoing, this study is also providing treatment blinded listings based on a data cutoff date of September 13, 2022. As agreed at the Pre-BLA meeting on July 11, 2022, the Applicant submitted blinded listings for deaths, discontinuations due to adverse events (AEs), and serious adverse events (SAEs), including all SAEs related to Amyloid Related Imaging Abnormality-edema (ARIA-E), ARIA-Related Imaging Abnormality Hemorrhage (ARIA-H), skin rash, and other hypersensitivity reactions, together with subject narratives and case report forms for those events in blinded ongoing studies Study BAN2401-G000-303 (Study 303; AHEAD 3-45) and DIAN-TU. This review focuses on results from subjects in whom lecanemab was administered as an intravenous (IV) infusion once every two weeks. In Study 201 OLE, after completion of 18 months of receiving lecanemab once every two weeks the subjects had a choice to continue with study treatment with lecanemab 10mg/kg once every 4 weeks or once every 3 months to complete up to 60 months of overall participation or until study drug is commercially available. In ongoing Study 301 OLE subjects receive lecanemab 10mg IV once every two weeks, or lecanemab subcutaneous (SC) administration once every week (if participating in the sub study) for up to 4 years. Another sub study in 301 OLE is exploring weekly subcutaneous administration of lecanemab using an autoinjector (AI) device. The relevant parts of these studies that are the focus of this review are described further in Table **1**.

I will refer to the dose groups during this review where applicable as follows: placebo or PBO, for placebo and lecanemab or LEC10-BW for 10 mg/kg biweekly. Biweekly refers to administration once every 2 weeks. Lecanemab was administered as an intravenous (IV) infusion in subjects who were included in this review.

The Applicant defines the safety analysis set in Study 301 and 201 as all subjects who received at least 1 dose of study medication. In Study 301 Core, at least 1 laboratory, vital sign, or ECG measurement obtained subsequent to at least 1 dose of study drug was required for inclusion in the analysis of each specific parameter. To assess change from baseline, a baseline

measurement was also required. The Applicant's approach to defining the safety analysis set is adequate.

Table 1 Studies Supporting Safety in the Current Efficacy Supplement Review [1]

Study Number	Study Dates	Study Design/Population	Diagnosis, Main Inclusion Criteria	Study Treatments (Route of Administration)	No. of Subjects by Arm Randomized/Completed Sex Race *APOE4* Carrier Status Clinical Subgroup
BAN2401-G000-301 Core (Study 301 Core)	27 Mar 2019 to 25 Aug 2022	Double-blind, parallel-group, PBO-controlled, multicenter study to confirm the safety and efficacy of lecanemab in subjects with EAD (MCI) due to AD with intermediate likelihood/prodromal AD or mild AD dementia) and confirmed amyloid pathology indicated by positive amyloid load	Male and female subjects 50 to 90 years, inclusive MCI due to AD intermediate likelihood and mild AD dementia MMSE score ≥22 & ≤30 at Screening and Baseline Positive biomarker for brain amyloid pathology as indicated by 1 of the following: • PET assessment of imaging agent uptake into brain • CSF assessment of t-tau/Aβ[1-42]	PBO (IV) LEC10BW (IV)	PBO Randomized/completed: 897/757 Sex: 421M, 476F Race: 696W, 150A, 25B, 12O, 12MI, 2NAM, 0NH *APOE4* carrier: 611Y (133HO, 478HET), 286N Clinical Subgroup: 555MCI, 342Mild AD LEC10-BW Randomized/completed: 898/729 Sex: 436M, 462F Race: 685W, 153A, 22B, 21O, 16MI, 0NAM, 1NH *APOE4 carrier*: 620Y(141HO,479HET), 278N Clinical Subgroup 552MCI, 346Mild AD *APOE4* carrier: 620Y (141HO, 479HET), 278N Clinical Subgroup: 552MCI, 346Mild AD
BAN2401-G000-301 Open-label extension (Study 301 OLE Phase)	10 Nov 2020 to ongoing	OLE Phase to Study 301	Subjects who have completed the Core Study	LEC10-BW (IV) (or 720 mg SC as a weekly dose in optional substudy; SC data not included in this submission)	LEC10-BW Enrolled/completed: 964/0 Sex: 467M, 497F Race: 720W, 192A, 26B, 13O, 12MI, 1NAM *APOE4* carrier: 600Y (126HO, 474HET), 364N

[1] *Source: BLA761269-S001 Clinical Summary of Safety Table 1*

A = Asian, Ab = amyloid beta, AD = Alzheimer's disease, APOE4 = apolipoprotein E4, AI = autoinjector, B = Black, CDR = Clinical Dementia Rating; CN = Chinese; CSF = cerebrospinal fluid, CSR = clinical study report, DE = Germany, EAD = early Alzheimer's disease, ES = Spain, EYO = Estimated years from symptom onset, F = female, FR = France, HET = heterozygous, HO = homozygous, ISS = Integrated Summary of Safety, JP = Japanese, LEC = lecanemab, M = male, MAD = multiple ascending dose, MCI = mild cognitive impairment, MI = missing, MU = multiple, NAM = Native American, NH = Native Hawaiian or Other Pacific Islander, NL = Netherlands, O = other, OA = other Asian, IV = intravenous, MMSE = Mini Mental State Examination, N = no, OLE = open-label extension, PBO = PBO, PET = positron emission tomography, RAR = response adaptive randomization; SAD = single ascending dose, SC = subcutaneous, sCSR = synoptic clinical study report, t-tau =total tau, W = White (or Caucasian), Y = yes. a: Randomized set. b: Provided as available.

Study Number	Study Dates	Study Design/Population	Diagnosis, Main Inclusion Criteria	Study Treatments (Route of Administration)	No. of Subjects by Arm Randomized/Completed Sex Race *APOE4* Carrier Status Clinical Subgroup
					Clinical Subgroup: 627MCI, 337Mild AD
BAN2401- G000-201 Open-label extension	12 Dec 2018 to ongoing	OLE Phase to Study 201	Completed Visit 42 (Week 79) of the Core Study or who discontinued study drug during the Core due to select reasons	LEC10-BW (IV)	Clinical Subgroup: 34MCI, 18Mild AD LEC10-BW Enrolled/completed: 180/0 Sex: 93M/87F Race: 148W, 2B, 30A (including 21JP, 1CN, 8SK) APOE4 carrier: 125Y (28HO, 97HET), 55N Clinical Subgroup at the start of Core: 110MCI, 70Mild AD

Table 2 Ongoing Studies Providing Supportive Safety Data[1]

Study Number	Study Dates	Study Design/Population	Diagnosis, Main Inclusion Criteria	Study Treatments (Route of Administration)	No. of Subjects by Arm Randomized/Completed Sex Race *APOE4* Carrier Status Clinical Subgroup
BAN2401-G000-303 (Study 303)	14 Jul 2020 to ongoing	Study 303 consists of 2 trials (A45 and A3) under a single protocol and is a double-blind, parallel-treatment arm, PBO-controlled study to evaluate efficacy and safety of treatment with lecanemab in subjects with preclinical AD and elevated amyloid (A45 Trial) and subjects with early preclinical AD and intermediate amyloid (A3 Trial)	Male or female subjects 55 to 80 years, inclusive Known before Screening to have elevated brain amyloid according to previous PET or CSF testing A45 Preclinical AD with elevated amyloid MMSE score ≥27 Global CDR score of 0 A3 Early preclinical AD with intermediate amyloid MMSE score ≥27 at Screening	A45 PBO (IV) or LEC5-BW (IV) through 8 weeks (titration), then LEC10-BW (IV) through 96 weeks (induction), then LEC10-M (IV) through 216 weeks (maintenance) A3 PBO (IV), or LEC5-M (IV) through 8 weeks (titration), then LEC10-M (IV) through 216 weeks	Randomized: 322 subjects had been randomized (223 subjects in the A45 Trial, and 99 subjects in the A3 Trial). Demographics not available.

Study Number	Study Dates	Study Design/Population	Diagnosis, Main Inclusion Criteria	Study Treatments (Route of Administration)	No. of Subjects by Arm Randomized/Completed Sex Race *APOE4* Carrier Status Clinical Subgroup
			Global CDR score		
DIAN-TU-001 (ongoing)	22 Dec 2021 to ongoing	Randomized, double-blind, PBO-controlled platform trial of potential disease modifying therapies utilizing biomarker, cognitive, and clinical endpoints in dominantly inherited Alzheimer's disease	Male or female subjects 18 to 80 years, inclusive -10 to +10 EYO (secondary prevention population): within -10 to +10 estimated age at symptom onset, CDR 0 to 1, known eligible mutation carrier or at 50% risk -25 to -11 EYO (primary prevention population): within 11 to 25 years younger than their estimated age at symptom onset, CDR 0, known carrier or mutation in their family pedigree	E2814 (IV) 1500 mg every 4 weeks, or LEC10-BW (IV) through 48 to 80 months depending on time required for full recruitment.	No data report

The numbers are as of the data cutoff date of April 15, 2022. EYO: expected years to symptoms onset

Reviewer Comment: The study population for study 303 and DIAN-TU included subjects with preclinical AD (with no clinical symptoms), as opposed to early AD. The dosing regimen, given the study population of presymptomatic subjects and the resulting risk-benefit calculation, includes a different dosing schedule than the proposed indication and dose for early AD.

I will refer to studies by their number for the remainder of this document, modified with study type (Core, or OLE).

Study 301 CORE (also known as CLARITY AD) was a randomized, double-blind, placebo-controlled, parallel-arm study of 18 months duration, whose primary objective was to evaluate the efficacy of lecanemab in early AD, with amyloid and tau positron emission tomographic sub-studies. The double-blind study is being followed by an open-label extension (Study 301 OLE)

that is to last a maximum of 2 years. Patients with early AD (MCI due to AD with intermediate likelihood OR mild dementia due to AD, both diagnosed according to the 2018 National Institute on Aging-Alzheimer's Association [NIA-AA] criteria) were enrolled and randomized in a 1:1 ratio to lecanemab (10 mg/kg biweekly, administered by intravenous infusion) or matching placebo. Those enrolled were required to have an entry MMSE score ≥22, and elevated brain amyloid that is indicated by either of the following: positron emission tomography using an amyloid-binding ligand, or cerebrospinal fluid t-tau/Aβ42.

Safety assessments consisted of monitoring and recording all adverse events (AEs), monitoring of hematology, blood chemistry, urinalysis, measurement of vital signs, electrocardiograms (ECGs), and the performance of physical examinations during the study as specified in the schedule of assessments. Additional safety assessments included brain magnetic resonance imaging (MRI), anti-drug antibody (ADA) assays, and Columbia-Suicide Severity Rating Scale (C-SSRS). An approach to detecting and managing amyloid related imaging abnormalities was specified and will be further discussed under 7.5.1 ARIA.

Study 301 Core had an 18-month treatment duration followed by a 3-month follow-up period or an optional 60-month OLE phase. The study was blinded until all subjects completed 18 months of treatment. All subjects who completed 18 months of Core study (but necessarily completed all the study treatments) transitioned into the Study 301 60-month OLE phase, provided they met the inclusion/exclusion criteria. While in the majority of subjects this transition was relatively seamless with less than 30 days between the last dose of study drug in 301 Core, and first dose in 301 OLE, there were 111/1391 subjects in whom there was a gap of greater than 30 days. The majority had not completed all of the study treatments in 301 Core, but completed all 301 Core study visits, and transitioned to the OLE. In these subjects the mean gap in days between the last dose in the Core and first dose in the OLE was 56 days [SD 49 days, median 40 (range 31 to 486 days)]. The mean number of doses completed in 301 Core in these subjects was 36 (SD 4.40, median 38, range between 6-39) doses. Some of the main reasons for this gap included delays in study procedures (such as MRI or PET), ongoing AE or hospitalization, subject or caregiver availability, COVID-19 related closures or isolation. Study 301 OLE is currently ongoing and includes subcutaneous treatment sub studies. Only the IV treatment arm of Study 301 OLE will be discussed in this review. In addition to analysis of datasets provided by the Applicant, clinical study reports (CSRs), narratives of significant events including deaths, serious adverse events, discontinuations and special adverse events of interest will be reviewed. CRFs will be reviewed as needed.

The Applicant defined subjects who received at least one dose of lecanemab at any time in 301 Core, and/or the OLE phase as the lecanemab treated group. Safety in this review will be mainly evaluated in the following pools: 1) the placebo-controlled period of Study 301 Core, and 2) the OLE period. In some sections if relevant, results for the lecanemab-treated group (Core and OLE combined), or new exposures (who were placebo in the Core) in the OLE will be presented as well.

Study 201 OLE was reviewed as part of the Safety Review of the original submission under BLA761269 with a data cutoff of December 21, 2021. In the present review, cumulative 201 OLE data with a data cutoff of December 1, 2022, were reviewed. Study 201 OLE is the extension period of Study 201 Core which represented the main safety data for submission BLA761269.

There are some differences between the designs of Study 201 OLE and of Study 301 Core and OLE that may have impacted the safety findings in these two studies and in turn impacted the ability to compare the safety results from these two studies. While majority of the inclusion/exclusion criteria were similar, there were differences in management of ARIA-E which are outlined under Section 12.1.8. In Study 301 Core and OLE, treatment was stopped for any symptomatic ARIA-E, or asymptomatic radiographically moderate or severe ARIA-E, and resumed when ARIA-E resolved radiographically and symptoms resolved clinically. Treatment was discontinued for radiographically severe ARIA-E that was associated with an SAE. In 201 OLE, treatment was resumed for asymptomatic mild and moderate ARIA-E and was only temporarily stopped for symptomatic ARIA-E of any radiographic severity. Study drug was not discontinued in 201 OLE if a severe ARIA-E was associated with an SAE. The approach to management of ARIA-H was similar across these studies.

7.2. Review of the Safety Database

7.2.1. Overall Exposure

The current total number of subjects, with a data cutoff date of December 1, 2022, that have been exposed to at least one dose of lecanemab at any dose and have unblinded safety data is 2345. Of these, the exposure at the intended dose of IV lecanemab was 2090[2] total, 1604 for 6 months or more, 1261 for 1 year or more, and 965 for at least 18 months as of the 90 day safety update. These exposure numbers meet the ICH guideline for exposure requirements for drugs intended for long-term treatment.[3]

The ongoing Study 303 and DIAN-TU-001 studies are not considered under the exposure numbers as these studies are ongoing and remain blinded.

There are 2345 subjects who have been exposed to the study drug at any dose and duration and contribute to the safety data set with unblinded safety data (**Table 3**).

[2] Number is obtained by adding the following n (study number): 7 (104), 12 (101), 161 (LEC10-BW, 201 Core), 253 (LEC-10 M, 201 Core), 45 (201 OLE), 898 (301 Core), 714 (301 OLE)
[3] https://database.ich.org/sites/default/files/E1_Guideline.pdf

Table 3 Safety Population, Size and Denominators

Safety Database for the Study Drug[a] Individuals exposed to lecanemab at any dose and duration in completed trials N=2345[b]		
Total	New Drug	Placebo
Clinical Trial Groups	1616[c]	1167[d]
Uncontrolled Trials	759[e]	N/A

[a] Study drug in this table refers to iv formulation of lecanemab
Numbers are obtained by adding the following n (study number):
[b]19 (104)+ 60 (101) + 609 (201 Core)+45 (201 OLE) + 898 (301 Core) + 714 (301 OLE)
[c] 19 (104)+ 60 (101) + 609 (201 Core) + 30 (004) +898 (301 Core)[d] 245 (201 Core) + 20 (101) + 5 (104) + 897 (301 Core)
[e] 45 (201 OLE) + 714 (301 OLE) based on 90-day updated data with data cutoff of December 1, 2022 sponsor Tables 14.3.1.1 and 14.3.2.1.1

Table 4 Duration of Exposure at the Dose Proposed Based on the Division's Approach

	Study 201 Core and OLE	**Study 301 Core and OLE**	**Total**
At least 6 months of exposure	242[1]	1362[2]	1604
At least 12 months of exposure	222[3]	1039[4]	1261
At least 18 months of exposure	194[5]	771[6]	965

Cutoff date of December 01, 2022
Numbers are obtained by adding the following drug exposures n (study number):
[1] *110 (Core) + (132)*
[2]816 (Core+ OLE in LEC10BW group) +546 (OLE new exposure)
[3] 99 (Core) + 123 (OLE new exposure to proposed dose
[4]765 (Core+ OLE in LEC10BW group) + 274 (OLE new exposure)
[5]88 (Core) + 106 (OLE)
[6]698 (CORE) + 73 (OLE) + 45 (OLE new exposure)
In Study 301 for subjects that received LEC10BW in the Core, exposure was calculated by adding exposure from Core and OLE periods. For those who received placebo in 301 Core, only exposure during 301 OLE was included. 90-day updates implemented based on the Applicant's 301 OLE Tables 14.3.1.1 and 14.3.2.1.1

In the 201 Core study due to the gap period of 9 to 56 months, and the fact that doses other than the proposed dose were used in 201 Core, a subject's exposure to study drug at the proposed dose of drug was captured either under 201 Core or 201 OLE, but not both. Of the subjects who were exposed to the proposed dose in 201 Core and 201 OLE, the duration of

exposure was captured either under Core or OLE, depending on which exposure was longer.

In Study 301, for those who received lecanemab in the Core study total exposure was calculated by adding exposure during the Core and OLE periods. For those who received placebo during 301 Core and entered the OLE, exposure was calculated only for the duration of the 301 OLE study. For those that had a gap period > 30 days between the last dose in Core and first dose in OLE the approach to calculating exposure remained the same. Total exposure to lecanemab was 898 in 301 Core, 1385 in 301 OLE, and 1612 subjects in 301 Core and OLE combined.

One of the safety concerns in the original submission of BLA761269 was the small number of subjects who were carriers of the ApoE ε4 allele who were exposed to the proposed dose of study drug. Due to changes in the protocol early on in 201 Core, only 49 subjects who were ApoE ε4 carriers were exposed to one or more doses at the proposed dose, only 18 to 6 months or more, and 12 to 12 months and more. In Study 301 Core and OLE combined 1116 ApoE ε4 carriers received at least one dose, 883 received 6 months or more, 691 received 12 months or more and 517 received 18 months or more (Source: 301 OLE CSR Table 14 .3.1.1.1, with data cutoff date of December 1, 2022).

7.2.2. Relevant Characteristics of the Safety Population

The proposed target population is patients with early AD, which is defined as patients with MCI or mild dementia due to AD. Similar to Study 201, Study 301 enrolled patients with early AD.

Since the placebo-controlled arm of Study 301 will constitute the main safety database, the demographics of this study are summarized below (Table 5). Baseline characteristics such as age, sex, race, ApoE ε4 genotype, use of symptomatic medications, age at onset of symptoms were similar across the two study arms.

Table 5 Demographic and Baseline Characteristics -Study 301 Core (Safety Analysis Set)

Category	PBO (N=897)	LEC10-BW (N=898)	Combined Total (N=1795)
Age (year)[a]			
Mean (SD)	71.1 (7.8)	71.4 (7.9)	71.3 (7.8)
Min, Max	50, 90	50, 90	50, 90
Age groups (n%)			
< 65 years	178 (19.8)	175 (19.5)	353 (19.7)
≥65,<80 years	610(68)	593(66)	1203(67)
≥80 years	109(12.2)	130(1.5)	239(13.3)
Sex, n (%)			
Male	421 (46.9)	436 (48.6)	857 (47.7)
Female	476 (53.1)	462 (51.4)	938 (52.3)
Race, n (%)			
White	696 (77.6)	685 (76.3)	1381 (76.9)

Category	PBO (N=897)	LEC10-BW (N=898)	Combined Total (N=1795)
Black or African American	25 (2.8)	22 (2.4)	47 (2.6)
Asian	150 (16.7)	153 (17.0)	303 (16.9)
American Indian or Alaskan Native	2 (0.2)	0	2 (0.1)
Native Hawaiian or Other Pacific Islander	0	1 (0.1)	1 (0.1)
Other	12 (1.3)	21 (2.3)	33 (1.8)
Missing	12 (1.3)	16 (1.8)	28 (1.6)
Ethnicity			
Not Hispanic or Latino	759 (84.6)	744 (82.9)	1503 (83.7)
Hispanic or Latino	114 (12.7)	117 (13.0)	231 (12.9)
Missing	24 (2.7)	37 (4.1)	61 (3.4)
Region			
Asia-Pacific	148 (16.5)	146 (16.3)	294 (16.4)
Europe	214(23.9)	215 (23.9)	429 (23.9)
North America	535(59.6)	537 (59.8)	1072 (59.7)
APOE4 carrier status (Laboratory), n (%)			
Carriers	611 (68.1)	620 (69.0)	1231 (68.6)
Heterozygous	478 (53.3)	479 (53.3)	957 (53.3)
Homozygous	133 (14.8)	141 (15.7)	274 (15.3)
Noncarriers	286 (31.9)	278 (31.0)	564 (31.4)
Use of AD symptomatic medication at Baseline (CRF), n (%)			
Yes	477 (53.2)	466 (51.9)	943 (52.5)
No	420 (46.8)	432 (48.1)	852 (47.5)
Clinical subgroup (CRF), n (%)			
MCI due to AD	555 (61.9)	552 (61.5)	1107 (61.7)
Mild AD dementia	342 (38.1)	346 (38.5)	688 (38.3)
Number of years of disease since diagnosis			
n	895	898	1793
Missing	2	0	2
Mean (SD)	1.34 (1.538)	1.43 (1.527)	1.38 (1.533)
Median	0.80	0.80	0.80
Min, Max	0, 11.2	0, 10	0, 11.2
Number of years since onset of symptoms			
n	897	897	1794
Missing	0	1	1
Mean (SD)	4.15 (2.518)	4.14 (2.354)	4.15 (2.437)
Median	3.60	3.80	3.70
Min, Max	0.5, 25.6	0.4, 21.2	0.4, 25.6
Age at onset of symptoms (Years)			
n	897	897	1794
Missing	0	1	1
Mean (SD)	67.6 (8.04)	68.0 (8.08)	67.8 (8.06)
Median	68.3	68.8	68.6
Min, Max	29.9, 86.9	38, 85.7	29.9, 86.9

Source: Summary of Clinical Safety Table 15. Percentages are based on the total number of subjects in relevant treatment group.AD = Alzheimer's disease, APOE4 = apolipoprotein E4, CRF = case report form, IxRS = interactive voice and web response system, MCI = mild cognitive impairment, Min = minimum, Max = maximum. A: Age is calculated at Date of Informed Consent. Source: Study 301 Core CSR Table 14.1.4.1.3.

Reviewer comment: Patients with moderate or severe dementia due to AD were not eligible for enrollment in Study 301. Therefore, the safety outcomes from this study, which enrolled subjects

with early AD (MCI and mild dementia due to AD), may not represent the risks in patients with moderate or severe dementia due to AD.

The following comments compare demographics of the 301 Core with the general population with AD. The data for the general population is obtained from the Alzheimer's Association 2021 Alzheimer's Disease Facts and Figures Report.[4]

The majority of patients in 301 Core were > 65 years old, and exposure to those under 65 years old was limited in 301 Core.

In the general population, the reported prevalence of ApoE ε4 allele carriership in patients with AD ranges between approximately 30-70 % depending on the study population, with patients with Northern European ancestry having a prevalence of ~ 60 %. [5] *The prevalence of ApoE ε4 allele carriership in Study 301 was representative of the general population of patients with AD.*

Compared with non-Hispanic Whites, Blacks are at increased risk for AD.[4] *In Study 301 Black or African Americans were underrepresented compared to the U.S. population limiting the generalizability of the safety observations*.

7.2.3. Adequacy of the safety database:

The current total number of subjects in Phase 1-3 studies exposed to at least one dose of lecanemab and have unblinded safety data is 2154. In study 301 Core, which constitutes the main safety database for this application, 811 subjects were exposed to LEC10-BW for at least 6 months, 757 for at least 12 months, and 513 for at least 18 months. These numbers exceed the ICH guidelines of 300 patients for 6 months, and 100 patients for 1 year at the clinically relevant dose. The safety database is adequate to assess the safety of the lecanemab 10 mg/kg biweekly.

7.3. Adequacy of Applicant's Clinical Safety Assessments

Overall the Applicant's clinical safety assessment are adequate. The exception to this is that in Study 201 Core, there was a signal for transiently reduced lymphocyte count after an infusion. In Study 301 Core, blood samples for laboratory tests were only collected prior to the infusion, and therefore, the earlier finding in 201 Core of transiently reduced lymphocyte count could not be assessed in the 301 Core Study.

[4] https://www.alz.org/media/Documents/alzheimers-facts-and-figures.pdf (Accessed 11/17/2022)
[5] *Ward A, Crean S, Mercaldi CJ, Collins JM, Boyd D, Cook MN, Arrighi HM. Prevalence of Apolipoprotein E4 Genotype and Homozygotes (APOE ε4/4) among Patients Diagnosed with Alzheimer's Disease: A Systematic Review and Meta-Analysis. Neuroepidemiology 2012;38:1-17.*

7.3.1. Issues Regarding Data Integrity and Submission Quality

Some of the aspects of the quality of the safety dataset were evaluated by the Office of Computational Science Jumpstart team. Overall, the application was well-organized, and information was easy to find. There were no major issues identified that would impact the data analysis and safety review.

7.3.2. Categorization of Adverse Events

Full details of the protocol defined safety analysis plan are found in Appendix Section 12.1.14.

In Study 301 an adverse event (AE) was defined as any untoward medical occurrence in a patient or clinical investigation subject administered an investigational product. An AE does not necessarily have a causal relationship with the medicinal product. For this study, the study drug was lecanemab.

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the investigational product (Note: Every sign or symptom was not listed as a separate AE if the applicable disease (diagnosis) was being reported as an AE).

All AEs, regardless of relationship to study drug or procedure, were recorded beginning from the time the subject signed the study informed consent form (ICF) through the last assessment (Visit 42 for the Core Study). AEs were collected for up to 3 months after the last dose or through the last assessment, whichever was longer. This included those subjects who discontinued from study drug and who returned for regularly scheduled visits where clinical assessments were conducted. All AEs were followed for 90 days after the subject's last dose, or until resolution, whichever came first. All SAEs were followed to resolution or, if resolution was unlikely, to stabilization.

Abnormal laboratory values were not to be listed as separate AEs if they were considered to be part of the clinical syndrome that was being reported as an AE.

AEs were graded on a 3-point scale (mild, moderate, severe) by the investigator, defined as follows:

- Mild discomfort noticed, but no disruption of normal daily activity
- Moderate discomfort sufficient to reduce or affect normal daily activity
- Severe incapacitating, with inability to work or to perform normal daily activity.

In 301 Core, a TEAE was defined as an AE that emerges during treatment or within 90 days of the last dose of study drug, having been absent at pretreatment (baseline) or:

- Reemerges during treatment, having been present at pretreatment (baseline) but stopped before treatment, or

- Worsens in severity during treatment relative to the pretreatment state, when the AE is continuous.

In the combined 301 Core and OLE Study, similar to the combined 201 Core and OLE ISS dataset, the Applicant defined a TEAE as emerging within 30 days of last administration

Reviewer Comment: A TEAE definition of occurring within 30 days after the last dose of study drug is reasonable, given the 5-day half-life of study drug (albeit a longer pharmacodynamic (PD) half-life). This was the approach used in this review, and by the Applicant when creating the treatment emergent flags in the adverse event datasets.

The overall approach to assessing relationship of AE to study treatment is acceptable and was based on the following:

- Temporal relationship of the onset of the event to the initiation of the study treatment
- The course of the event, especially the effect of discontinuation of study treatment or reintroduction of study treatment, as applicable
- Whether the event was known to be associated with the study treatment or with other similar treatments
- The presence of risk factors in the study subject known to increase the occurrence of the event
- The presence of non-study, treatment-related factors that are known to be associated with the occurrence of the event.

An SAE was defined as any untoward medical occurrence that at any dose:

- Resulted in death
- Was life-threatening (i.e., the subject was at immediate risk of death from the AE as it occurred; this did not include an event that, had it occurred in a more severe form or was allowed to continue, might have caused death)
- Required inpatient hospitalization or prolongation of existing hospitalization
- Resulted in persistent or significant disability/incapacity
- Was a congenital anomaly/birth defect (in the child of a subject who was exposed to the study drug).

Other important medical events that may not have been immediately life-threatening or resulted in death or hospitalization but, when based on appropriate medical judgment, may have jeopardized the subject, or may have required intervention to prevent one of the outcomes in the definition of SAE listed above were also to be considered SAEs. Medical and scientific judgment was exercised in deciding whether expedited reporting was appropriate in such situations.

In addition to the above, other events associated with special situations included pregnancy or exposure to study drug through breastfeeding; AEs associated with study drug overdose, misuse, abuse, and medication error. These events associated with special situations were

captured using the SAE procedures but were considered as SAEs only if they met one of the above criteria. All AEs associated with special situations were reported on the CRF whether or not they met the criteria for SAEs.

Study specific AEs of interest included ARIA-E, ARIA-H (macrohemorrhages, superficial siderosis, or new cerebral microhemorrhages), infusion related reactions, hypersensitivity reactions, and a "yes" response to C-SSRS suicidal ideation Type 4 or 5.

Adverse events were coded using MedDRA Version 25 for Study 301 and MedDRA Version 24.0 for the OLE. There were 109 records (21%) that were mismatched for the Preferred Term and 5 records (0.99%) mismatched for the Body System and Organ Class Term between 201 Core and ISS. Mismatches caused by differences in the MedDRA versions were reviewed individually, to identify any mismatch that may impact AE identification. None was found to impact the safety assessment.

I reviewed the reported terms for adverse events of special interest and their mapped MedDRA Lower Level and MedDRA Preferred Terms. Overall, I found that the Applicant's coding appeared to be adequate. I note that if a cerebral microhemorrhage was not treatment emergent, the dictionary derived term: "cerebral microhemorrhage" was used. If a cerebral microhemorrhage was treatment emergent, then it was captured under "ARIA-H cerebral microhemorrhage or hemosiderin depositions". Cerebellar microhemorrhage was used for both treatment emergent and non-treatment emergent microhemorrhages but were included under dictionary derived terms that constitute ARIA-H. In one case, a reported term of "Frequent giddiness" was captured under dizziness preferred term.

7.3.3. Routine Clinical Tests

In both Study 301 Core and OLE, safety assessments included monitoring and recording all AEs and SAEs; regular monitoring of hematology, blood chemistry, and urine values; periodic measurement of vital signs and ECGs; and performance of physical examinations and suicidality assessments. Additional safety assessments included brain MRI, and anti-BAN2401 antibody assays. Details are provided in Appendix 12.1.15.

Laboratory Tests

The Applicant used the Common Toxicity Criteria for Adverse Events v4.0.3 (CTCAE) published on June 14, 2010, to determine grade for laboratory tests (Appendix Table).

The Applicant relied on the CTCAE criteria to identify subjects with treatment-emergent markedly abnormal laboratory values (TEMAVs). Since the CTCAE criteria are created for clinical trials in cancer, reliance on the CTCAE grading alone for some of the laboratory values may miss some clinically significant laboratory findings that are not included in the CTCAE grading. For

example, elevation in white cell count, is not captured by the CTCAE grading system above, but may be important in non-cancer trials.

Reviewer Comment: To be able to capture clinically significant abnormal values that may not be captured as part of the CTCAE grading system (such as a shift to abnormally high neutrophil count), the review of laboratory values will include thresholds identified by the FDA as clinically significant.

7.4. Safety Results

7.4.1. Deaths

In Study 301 CORE, there was not an excess of deaths in the lecanemab-treated group compared to placebo (0.7% in the lecanemab vs 0.8% in placebo for deaths for which the precipitating event occurred within 30 days after the last dose, and excluding two deaths which occurred more than 30 days after last study treatment administration, one each on placebo and lecanemab) (Table 6). As of a 90-day data cutoff date of December 1, 2022, a total of 26 deaths (inclusive of deaths that occurred more than 30 days after last study treatment administration) have occurred in patients receiving lecanemab across the lecanemab clinical development program. This included 10 deaths in lecanemab-exposed subjects in the 201 Core (5) and OLE (5), 7 deaths in 301 Core, and 9 deaths in 301 OLE. No deaths have been reported in Study 303, Study 101, Study 104, and Study 004.

None of the deaths in 301 Core was preceded by ARIA-E or ARIA-H (microhemorrhage or superficial siderosis). However, there are three deaths which occurred during the 301 OLE, two of which (b) (6), (b) (6) were associated with a treatment emergent cerebral hemorrhage and one death ((b) (6) occurring after symptomatic ARIA-E with seizure and related complications. These three cases will be described in more detail below.

Reviewer Comment: In the two deaths in 301 OLE ((b) (6) and (b) (6) described below, the subjects had underlying moderate and severe cerebral amyloid angiopathy respectively, and experienced neurological symptoms shortly after starting study drug, ultimately leading to hospitalization and death with autopsy showing necrotizing vasculitis. I cannot rule out the possibility that lecanemab-induced amyloid removal in patients with underlying advanced cerebral amyloid angiopathy triggers a CAA related inflammation /vasculitis like presentation.

I recommend that a statement be added to the label that patients with radiographic findings suggestive of amyloid angiopathy were excluded from the clinical trials, that the presence of an ApoE ε4 allele is associated with CAA which has an increased risk for intracerebral hemorrhage, and that caution should be exercised when considering us of lecanemab in patients with factors that indicate an increased risk.

As of data cutoff of December 1, 2022, the incidence of death by person-years of exposure in 301 Core (inclusive of nontreatment emergent deaths) was 5.9 /1000 person years (7/1177.9) on lecanemab, and 6.5/1000 person-years (8/1233) on placebo. In the subjects exposed to lecanemab in 301 Core and OLE the incidence of death for lecanemab was 6.9/1,000 person years (16/2331.2) person years.[6] This does not exceed the reported incidence of death from AD in the US of 133.8/1,000 person years.

Reviewer Comment: The above numbers should be considered with keeping in mind the limitation of comparing death rate of subjects in the early stage of AD, with the overall AD population inclusive of later stages, as those who are at later stages have a higher morbidity and those that are able to participate in clinical trials are healthier in general.

Deaths in the Study 301 Core and OLE

Study 301 Core

Overall there were 15 deaths out of 1795 subjects in the placebo controlled 301 Core study (inclusive of deaths occurring 30 days after the last dose of study drug) as shown in the table below. There was not a higher incidence of deaths in the lecanemab arm compared to placebo in the placebo-controlled period of study 301 (Table 6). One death each in the lecanemab and placebo arms occurred beyond 30 days after the last dose of study drug administration.

Table 6 Incidence of Deaths in the Placebo Controlled Period of Study 301

Study	Lecanemab	Placebo
301	7/898 (0.8 %)	8/897 (0.9%)

In the placebo-controlled period of Study 301, the preferred terms of adverse events with fatal outcomes in the lecanemab arm were: COVID-19, death, myocardial infarction, cerebrovascular accident, diabetic ketoacidosis, metastases to meninges, and respiratory failure. In the placebo group, the preferred terms of adverse events with fatal outcome were acute respiratory failure, cardio-respiratory arrest, COVID-19, death, hemorrhage intracranial, metastases to bone, myocardial infarction, pancreatic carcinoma. None of the cases of death was preceded by ARIA. (Table 7)

Table 7 Deaths in Lecanemab Treated Patients in 301 Core

[6] 120-day cut-off updated death by person-years provided by the sponsor on October 26, 2022 in response to an IR from the Agency.

Subject ID	Age at death, Sex, Race	Reported Term for Adverse Event with fatal outcome	Risk Factors
(b) (6)	87-year-old white female	Death (unknown cause)	Age
	80-year-old male	Stroke, acute symptomatic	Hypertension, hyperlipidemia, Atrial fibrillation Coronary Artery disease
	71-year-old while male	Suspected myocardial infarction	DM II, hypertension, hyperlipidemia, coronary artery disease
	89-year-old white female	Respiratory failure	Atrial fibrillation, coronary artery disease, Diabetes, hypertensive heart disease, hypertension, hyperlipidemia, pulmonary hypertension, AV block, COPD, Pulmonary embolism Pneumonia
	78-year-old white male	Lymphomatous Meningitis	Age
	78-year-old white male	Respiratory Tract Infection SARS-COVID 19	Age, Diabetes, coronary artery disease
	80-year-old white male	Diabetic Ketoacidosis (36 days after last dose)	Diabetes, Urinary tract infection, coronary artery disease.

I reviewed the narratives of these deaths and except for one subject (b) (6)), I could not identify a role of lecanemab in these deaths. Subject (b) (6) died 13 days after the 28th dose of study drug. The AE leading to death was listed as "death" in the ADAE dataset, and the narrative does not provide a cause of death nor describes the circumstances leading to her death. The only other AE in the ADAE dataset during her study participation was abnormal dreams. Given lack of information, I am unable to determine the relatedness of the study drug to this patient's death. See Appendix Section 12.1.3 for the narratives of these subjects.

Study 301 OLE

As of the 90-day data cutoff of December 1, 2022, the incidence of death in the 301 OLE was 0.7% (9 out of 1385). In the combined 301 Core and OLE dataset, the incidence of death was 1% (16 out of 1612; inclusive of one death where the precipitating event occurred beyond 30 days after the last dose of study drug).

The preferred terms of adverse events with fatal outcomes for deaths during the 301 OLE period were the following occurring in one subject each unless otherwise indicated: Death, Myocardial infarction (MI), COVID 19 Pneumonia,COVID-19, Road Traffic Accident, Acute

Cardiac Failure, Cerebrovascular Accident, Cerebral Hemorrhage (n=2), and ARIA-E (Table 8) Four of these deaths were considered possibly related to study treatment per study investigator.

Table 8 Deaths in Lecanemab Treated Patients in 301 OLE

Subject ID	Age at death, Sex,	Reported Term for Adverse Event with Fatal Outcome	Risk Factors	Possibly caused by study drug per reviewer
(b) (6)	80-year-old female	Myocardial infarction	Hyperlipidemia Hypertension Cardiac murmur	No
	70-year-old male	COVID-19 with pneumonia	Diabetes, AD, hypertension	No
	83-year-old male	Acute cardiac failure	Narrative silent to any risk factors	No
	88-year-old male	Left occipital intracerebral macrohemorrhage (ARIA—H), symptomatic	Apixaban and aspirin use Falls	Yes
	65-year-old female	Acute multifocal intracerebral hemorrhage post tissue plasminogen activator	Underlying CAA Tissue plasminogen activator use	Yes
	79-year-old female	Possible Seizure, possible cerebrovascular accident	Underlying CAA	yes
	64-year-old female	Fatal car accident	None	No
	72-year-old female	Symptomatic suspected cerebrovascular accident	Presented with BP 180/100	Unable to determine
	86-year-old male	COVID19	Age	No

** Table includes death that occurred prior to the data cutoff of December 1, 2022. Subject (b) (6) who was diagnosed with pancreatic cancer on (b) (6), and died on (b) (6), was not included in the above table.*

I reviewed the narratives for the above patients. In 5 subjects ((b) (6)) I could not identify a clear role of study drug. In the case of subject (b) (6) who had cardiac risk factors for MI, the MI occurred 10 days after the first dose of lecanemab (as she received placebo during the Core). While I cannot entirely rule out a role of lecanemab because of the proximity of the MI to her first dose, given her multiple cardiovascular disease risk factors, it is more likely that the MI is related to her underlying risk factors. Subject (b) (6) (who received lecanemab during the Core period), was found unconscious in an open-air bath, 19 days after the 11th dose of study drug the OLE. No cardiac risk factors were noted in the narrative for this case. Given the multiple doses received, with no previous drug related adverse events, I could not identify a clear role of study drug in this case. Two subjects died of COVID-19 related complications ((b) (6) , one subject

(b) (6) due to a road car accident. I could not identify a role of study drug in these cases. See Appendix Section 12.1.3 for detailed narratives for these subjects.

Four deaths were possibly related to study drug. In two of these cases ((b) (6) I identified a role of study drug in the events leading to death. In subject (b) (6) there was insufficient information to make a clear causality assessment and in subject (b) (6) causality is not as clear cut due to other confounding events and medications.

(b) (6)
This was an 88 year old male with early AD who sustained a cerebral hemorrhage after the 9th dose of lecanemab in the 301 OLE and died 45 days after the last dose.. He was homozygous for ApoE ε3and had received placebo in the 301 Core Study. His relevant past medical history included atrial fibrillation, aortic stenosis, aortic valve replacement, coronary artery disease and coronary artery bypass surgery, history of lacunar stroke and hyperlipidemia. At his screening MRI there were three microhemorrhages in the following locations each, right cerebellum, left occipital region, and left frontal region. Relevant medications at the time he started participating in the 301 OLE were donepezil, apixaban, baby aspirin, tamsulosin and atorvastatin.

The patient sustained a fall on extension day 77 after 6 doses of study drug. He received the 9th dose of study drug on extension day 98 during the OLE. He had COVID-19 on day 98 and appeared to be treated with "protease inhibitors 150/100 mg/mg PO QD" for 5 days. On extension day 108 he experienced severe pain in his right arm and work up revealed a right ulnar pseudoaneurysm. Due to progressively worsening pain, he was admitted to the hospital where he received pain management with narcotics. He received an ultrasound guided thrombin injection into the right ulnar artery. Follow-up ultrasound showed a completely thrombosed pseudoaneurysm and he was discharged from the hospital. On extension day 114 he fell out of bed and bruised the left arm. During his study visit on extension day 116, he reported trauma to both arms and increased confusion. Lecanemab was not administered due to multiple medical concerns including past events of recurrent falls, COVID-19, and pneumonia. His study MRI on extension day 118 showed a left occipital cerebral hemorrhage > 1cm (with onset date based on symptoms of extension day 116). The subject also had ARIA-E in the left occipital area, as well as a new ARIA-H microhemorrhage in the left frontal area. All of these findings were deemed to be radiographically mild and symptomatic (confusion). Study drug was discontinued because of cerebral hemorrhage with last dose taken on extension day 98. Apixaban was stopped on extension day 119.

On extension day 124, the subject presented to an ER for chest pain shooting down his left arm. EKG changes and troponin elevation ruled in a myocardial infarction. He received heparin bolus and then a heparin drip which was discontinued due to the recent brain bleed. He was treated with aspirin and nitroglycerin and admitted to the telemetry unit. According to the study report for SAEs submitted as an amendment on May 26, 2023, clopidogrel was started on day 124. After a few days he was discharged with prn nitroglycerin for chest pain. On extension day 128

he had 4 TIA like events of garbled speech and right sided weakness. The next day, the subject enrolled in hospice, and continued treatment with clopidogrel as well as lorazepam for comfort and passed away on extension day 144.

A brain autopsy was performed on extension day 144. The autopsy report confirmed neuropathological AD, small vessel ischemic disease and a left occipital subacute intracerebral hemorrhage. While the report stated that the most likely etiology for the intracerebral hemorrhage was thought to be CAA, it also mentioned that there was absolutely no amyloid present in the vicinity of the hemorrhage. Microscopic examination did note minimal to mild amyloid angiopathy on immunohistochemical staining in the left occipital cortex, but no obvious plaque deposition. The neuropathologist hypothesized that the cause of the bleed may have been a potential side effect of lecanemab, CAA where the amyloid was removed by lecanemab, or a lingering effect of anticoagulation treatment or a combination of these. There also was evidence of subarachnoid hemorrhage, in the left occipital cortex, subacute to chronic which the neuropathologist felt was separate from the left occipital hemorrhage and may be explained by history of multiple falls. There was no evidence of inflammatory changes secondary to COVID-19. The pathologist also opined that there was no cause of death within the brain. The autopsy report did not provide a cause of death.

Reviewer Comment: In this case, the cerebral hemorrhage, and ARIA-E were identified on the same MRI and in the same brain region after the 9th dose of lecanemab, suggesting a potential role of study drug in both. Use of apixaban combined with aspirin may have contributed to the cerebral hemorrhage as well. . The presence of confounding medical events proximal to death, including myocardial infarction, and possible TIA in a patient with atrial fibrillation after discontinuation of anticoagulation, and patient's wishes to forego treatments and transition to hospice, precludes the ability to assess the direct role of study drug and cerebral hemorrhage to death.

(b) (6)

This was a 65 year old female with MCI who sustained multiple cerebral hemorrhages in the setting of tissue plasminogen activator administration, and died 8 days after the 3rd dose of lecanemab. She was homozygous for ApoE ε4 and had completed 301 Core on placebo. At the screening MRI prior to the OLE, she did not have any ARIA-E, microhemorrhages or superficial siderosis. She had underlying patent foramen ovale, which was discovered at autopsy. Based on the adverse event dataset she complained of headaches after each dose of lecanemab. She received the 3rd dose of study drug on extension day 29. On extension day 33, four days after the third dose of study drug, her husband noted that she had a blank stare and was talking incoherently. She was noted to have garbled speech and was taken to an ER. A CT of the head diagnosed an occlusive left-sided ischemic stroke due to an LM3 occlusion. Tissue plasminogen activator (tPA) was administered. Within 8 minutes after tPA she experienced a headache, and within 40 minutes she became agitated. Repeat imaging showed bilateral intracerebral hemorrhage with subarachnoid hemorrhage. EEG showed seizure activity. The tPA was stopped and cryoprecipitate and tranexamic acid were given for reversal of tPA. She was

treated with Haldol for agitation and lorazepam and Keppra for seizures. Her blood pressure was greater than 200 mmHg, for which she was started on nicardipine infusion. Her encephalopathy worsened and she was intubated. Per subject's wishes of not remaining on life support indefinitely she was extubated. According to the narrative provided by the Applicant, the MRI performed 3 days after the CT scan showed extensive multicompartmental intracerebral hemorrhages, innumerable hematomas, subarachnoid hemorrhage and right intraventricular hemorrhage with 5 mm leftward midline shift and bilateral uncal herniation. According to the clinical history provided in the autopsy report this MRI also showed an acute right thalamocapsular infarct. Eight days after the 3rd dose of study drug the subject expired shortly after extubation. On subsequent autopsy, the cause of death was identified as nontraumatic intracerebral hemorrhage. The autopsy showed extensive multifocal intraparenchymal hemorrhages, Alzheimer's disease neuropathologic changes, histiocytic/microglial reaction to parenchymal amyloid plaques, cerebral amyloid angiopathy with diffuse histiocytic vasculitis and focal fibrinoid necrosis. Vasculopathy was described as involving amyloid deposition within (but not outside) the blood vessel walls. The autopsy report states that moderate cerebral amyloid angiopathy was identified throughout by immunohistochemical staining, and also notes that fragmented cerebral amyloid angiopathy was present in areas involved by histiocytic vasculitis. There was no vascular territory infarct apart from an agonal lesion in the right posterior limb of the internal capsule which was felt to correspond to the acute right thalamocapsular infarct observed on MRI prior to death, and which was consistent with a small focus of agonal ischemia, unassociated with vasculitis or CAA. This subject's case was published in 2 publications.[7,8,9]

Reviewer Comment: While treatment with IV thrombolysis within 4.5 hours of acute ischemic stroke onset is associated with a 5 to 7 percent risk of intracerebral hemorrhage, I cannot rule out a role of study drug in this subject's case due to the fact that this incident occurred 4 days after the third dose of study drug in a subject who was on placebo previously, and the resulting intracerebral bleeding was extensive. While there is little experience with the use of thrombolytic drugs in subjects who are also receiving anti-amyloid monoclonal antibodies, there is some evidence to suggest that subjects with a diagnosis of CAA who receive thrombolytics have a higher risk of bleeding and a higher risk of more extensive bleeding with multilocular bleeds or bleeds outside the primary ischemic area.[10,11] This subject's MRI 4 months prior to this incident did not show cerebral microhemorrhages or superficial siderosis to suggest underlying

[7]Sabbagh M, van Dyck CH. Response to: Multiple Cerebral Hemorrhages in a Patient Receiving Lecanemab and Treated with t-PA for Stroke. NEJM, January 4, 2023. DOI: 10.1056/NEJMc2215907

[8] Reish NJ, Jamshidi P, Stamm B, Flanagan ME, Sugg E, Tang M, Donohue KL, McCord M, Krumpelman C, Mesulam M-M, Castellani R, Chou S H-Y. Multiple Cerebral Hemorrhages in a Patient Receiving Lecanemab and Treated with t-PA for Stroke. N Engl J Med 2023; 388:478-479
DOI: 10.1056/NEJMc2215148

[9] Castellani RJ, Shanes ED, McCord M, Reish NJ, Flanagan ME, Mesulam MM, Jamshidi P. Neuropathlology of Anti-Amyloid-β Immunotherapy: A Case Report. Journal of Alzheimer's Disease 93 (2023) 803–813.

[10] Block F, Dafotakis M. Cerebral Amyloid Angiopathy in Stroke Medicine. Dtsch Arztebl Int 2017; 114: 37–42. DOI: 10.3238/arztebl.2017.0037

[11] Felling RJ, Faigle R, Ho C-Y, Llinas RH, Urrutia VC. Cerebral Amyloid Angiopathy: A Hidden Risk for IV Thrombolysis. J Neurol Transl Neuroscie. 2014; 2(1):1034

CAA. Up to 90% of individuals with pathologic AD in general, and particularly ApoE ε4 homozygotes may have underlying CAA[12,13,14,15] , which does not always manifest as clinical or imaging findings during life.[16] Because she only had a CT in the emergency room, whether she had ARIA-E and ARIA-H prior to tPA administration is not known. The autopsy describes widespread necrotizing vasculitis involving blood vessels with cerebral amyloid angiopathy.[32] Whether the necrotizing vasculitis described in the autopsy report is a manifestation of CAA related inflammation (CAA-ri/vasculitis), which occurred spontaneously in this subject or whether study drug played a role is not entirely clear. Given that the subject had onset of symptoms of garbled speech and right sided weakness a few days after the third dose of study drug, in the absence of any known stroke risk factors, I cannot rule out the possibility that the study drug initiated an inflammatory /vasculitic event in this patient with a high burden of CAA which led to catastrophic bleeding after tPA administration. Identification of another subject ((b) (6) *who exhibited neurological symptoms shortly after starting study drug, and had similar autopsy findings, raises a concern that in subjects with underlying high burden of CAA, lecanemab may enhance an inflammatory reaction that manifests itself similar to CAA-ri/vasculitis. I note that the currently approved prescribing information for lecanemab alerts prescribers to exercise caution when administering antithrombotics or thrombolytics in patients during lecanemab treatment. In addition, as noted above, the label should recommend caution when considering use of lecanemab in patients that indicate an increased risk for intracerebral hemorrhage, including neuroimaging findings suggestive of CAA. This risk may be higher in those who have underlying CAA and are on anticoagulation. Risk benefit calculations should consider presence of a clinical diagnosis of CAA or CAA-ri/vasculitis or risk factors, such as ApoE ε4 homozygosity, for having co-morbid advanced CAA that has not manifested clinically.*

(b) (6)

This was a 79 year old female with AD who died 7 days after the 3rd dose of lecanemab due to severe symptomatic ARIA-E. She was an ApoE ε4 homozygote, who received placebo in 301 Core. The details of this case have been reported in a pre-print manuscript that has not been peer-reviewed. As of May 26, 2023, the Agency has received a copy of the MRI and autopsy

[12] Love S, Miners S, Palmer J, Chalmers K, Kehoe P. Insights into the pathogenesis and pathogenicity of cerebral amyloid angiopathy. Frontiers in Bioscience 14, 4778-4792, January 1, 2009.
[13] Ringman JM, Sachs MC, Zhou Y. Clinical Predictors of Severe Amyloid Angiopathy and influence of *APOE* Genotype in Persons with Pathologically Verified Alzheimer Disease. JAMA Neurol 2014; 71:878-883. doi:10.1001/jamaneurol.2014.681
[14] Yu L, Boyle PA, Nag S, Leurgans S, Buchman AS, Wilson RS, Arvanitakis Z, Farfel JM, De Jager PL, Bennett DA, Schneider JA. APOE and Cerebral Amyloid Angiopathy in Community Dwelling Older Persons. Neurobiol Aging. 2015 November; 36(11): 2946–2953. doi:10.1016/j.neurobiolaging.2015.08.008Jäkel, Lieke et al. Prevalence of Cerebral Amyloid Angiopathy: A Systematic Review and Meta-analysis. Alzheimer's and Dementia.
[15] Brenowitz WD, Nelson PT, Besser LM, Heller KB, Kukull WA. Cerebral amyloid angiopathy and its co-occurrence with Alzheimer's disease and other cerebrovascular neuropathlogic changes. Neurobiol Aging 2015; 36 (2702-2708). doi:10.1016/j.neurobiolaging.2015.06.028.
[16] Jäkel L, De Kort A, Schreuder F, and Verbeek M. Prevalence of cerebral amyloid angiopathy: A systematic review and meta-analysis. Alzheimer's Dement.2022;18:10–28. https://doi.org/10.1002/alz.12366.

report. According to the pre-print manuscript [17] a study MRI prior to the OLE showed a left parietal meningioma < 1 cm and 4 small cerebral microhemorrhages. According to the Applicant's central and local MRI readers, there were no microhemorrhages on this MRI. The Agency reviewed the pre-treatment MRI before the OLE and confirms at least 3 cerebral microhemorrhages. Her relevant past medical history included chronic kidney disease, aortic atherosclerosis, hyperlipidemia. She had the third dose of study drug on extension day 31. According to hospital records, subject's friend and family reported that the subject had been experiencing brain fog, headaches and fatigue related to lecanemab. According to the pre-print manuscript, the subject's study partner reported that the subject had been complaining of headaches occurring about an hour after each infusion, causing her to spend a day or two in bed recovering. It was also reported that after the third dose of study drug she began to experience progressively worsening memory impairment described as brain fog. The AE dataset lists headache as an adverse event occurring after the 2nd dose for which the outcome is listed as resolved. According to the hospital records, one week after the third dose the subject experienced a sudden onset of slurred speech, and left gaze deviation, and left side weakness, reported in the original CIOMS as a possible cerebrovascular accident and possible seizure. According to the pre-print manuscript the seizure began with left head and gaze version and left sided tonic contraction which evolved into a 30-second generalized convulsion. Upon EMS arrival her oxygen saturation was found to be in the 80s, Glasgow coma scale was less than 8. She was sedated and intubated. In the hospital a CT of the brain showed no intracranial hemorrhage, mass effect or midline shift. She was evaluated for an acute stroke but was felt to not be a good candidate for tPA. She was hospitalized for possible stroke and possible seizure. She was noted to be in paroxysmal atrial fibrillation on telemetry. She was started on aspirin, Keppra and empirical antibiotics. She had a repeat CT head on extension day 39 which did not show any acute hemorrhage, infarct or mass, and showed extensive demyelination in the frontal and parietal lobes, unchanged from prior CT. A CT brain perfusion scan/CTA showed no large vessel occlusion and symmetric perfusion without evidence of cerebral ischemia. EEG showed frontal dominant rhythmic activity, possibly due to structural abnormalities, diffuse background slowing consistent with metabolic encephalopathy and no epileptiform activity. She was started on iv heparin for atrial fibrillation.

On extension day 40, an MRI with and without contrast obtained at the hospital was reported as showing the following in the hospital records: No midline shift or acute infarct; 2) Hemosiderin stain noticed along the left temporal lobe and bilateral frontal lobes which may represent a metastatic lesion or focal area of cortical hemorrhage; 3) Extensive areas of low attenuation in the periventricular and subcortical white matter which could represent edema, demyelination or microvascular disease, more prominent on the temporal lobes and parietal lobes. Cytotoxic edema was another consideration. Based on the above the subject was considered to have possible cerebral edema. A follow up MRI was obtained with contrast to

[17] Solopova E, Romero-Fernandez W, Harmsen H, Ventura-Antunes L, Wang E, Shostak A, Maldonado J, Donahue M, Schultz D, Coyne T, Charidimou A, Schrag M. Fatal Iatrogenic Cerebral Amyloid-Related Encephalitis in a patient treated with lecanemab for Alzheimer's disease: neuroimaging and neuropathology. medRxiv 2023.04.26.23289061; doi: https://doi.org/10.1101/2023.04.26.23289061.

better assess the meningioma. Based on the hospital records, this was reported to show the interhemispheric fissure meningioma, and also stated that there was no other pathologic intraparenchymal lesion. The pre-print manuscript describes the post treatment MRI to show 30 microhemorrhages all in a cortical juxtacortical distribution and most within areas of edema in the temporal, parietal and occipital lobes. Based on an updated safety report to IND 105081 from the Applicant dated May 18, 2023, the study central MRI reader identified severe ARIA-E and 51 microhemorrhages without macrohemorrhage, midline shift, mass effect or herniation on the post-treatment hospital MRI. IV heparin was discontinued, and the subject was started on solumedrol 1 gram daily for 3 days for possible cerebral edema. A transthoracic echocardiogram was performed which was normal. Based on discussions with the subject's family members and her living will confirming a "Do Not Resuscitate" stipulation, it was decided to extubate the subject and place her on BiPAP and manage her conservatively. On extension day 41, her chest x-ray showed new airspace opacities through the right lung and perihilar left lung. Based on this and elevated white blood cell counts, she was diagnosed with aspiration pneumonia and started on antibiotics. On extension day 43 she developed respiratory failure and was transitioned to comfort measures only, discontinuing the BiPAP and passed away the following day. The authors of the pre-print manuscript mention that postmortem imaging revealed more extensive hemorrhages. On neuropathological examination provided to the Agency on May 25, 2023, cause of death was identified as atherosclerotic and hypertensive heart disease with bronchopneumonia with diffuse alveolar damage (acute respiratory distress syndrome) contributing. The neuropathological examination of the brain showed the cerebrum to be symmetrical and moderately edematous characterized by widened and full gyri and narrowed sulci. The bilateral unci and cerebellar tonsils were found to have pressure grooves. The pathology report describes abundant neuritic plaques of AD, and while most were entirely typical, 21% appeared to have been "cleared" characterized by a distinctive rosette of dystrophic neurites without the typical central amyloid deposits. The report also states that 24% of the plaques had minimal staining of amyloid deposits. The beta-amyloid stains identified diffuse mural vascular amyloid diagnostic of severe cerebral amyloid angiopathy. Small vessels with petechial hemorrhages contained significant beta-amyloid deposits. The report notes marked perivascular inflammation, including microglia and multinucleated giant cells with fibrinoid necrosis and petechial hemorrhages and identifies this as CAA related inflammation (CAA-RI).

Reviewer Comment:
I cannot rule out a role of study drug in this subject's hospitalization and ultimate death based on the fact that symptoms began after the first 3 doses of study drug in a subject who was homozygous for the ApoE ε 4 allele, the reported imaging findings from hospital records, and the pre-print manuscript. The review team from the FDA was able to review the pretreatment study MRI, as well as the hospital MRI, and was able to confirm the presence of at least 3 microhemorrhages on the pre-treatment MRI, and on hospital post treatment MRI the presence of cerebral edema consistent with ARIA-E, and increased ARIA-H microhemorrhages. The autopsy results of this subject describe severe amyloid angiopathy with features suggestive of

CAA-related inflammation/vasculitis. This finding is very similar to the autopsy findings of subject (b) (6) *described above. It is plausible that amyloid removal with lecanemab in those with underlying CAA increases the risk of occurrence of a CAA-ri like presentation. While the subject's ultimate death is due to aspiration pneumonia, it is highly likely that the study drug played a role in her death, causing symptomatic ARIA-E and ARIA-H that triggered the events leading to hospitalization, including seizure, aspiration pneumonia and death. This case further supports a statement be added to the label that providers should consider the risk benefit calculation differently when considering administration of lecanemab in ApoE ε4 homozygotes who are at increased risk of having co-morbid severe amyloid angiopathy.*

(b) (6)

This is a 73 year old female with MCI, died 10 days after the 35th dose of lecanemab due to a cerebrovascular accident. She had an ApoE ε3/ε3 genotype, and had received lecanemab during her participation in 301 Core. Her past medical history was significant for MCI, hysterectomy and uterine prolapse. The subject received the 9th dose of study drug on extension day 140. On extension day 149, she presented to the emergency room with mild dysarthria, and a 2-day history of diarrhea. At that time, she was alert, conscious and cooperating, but found to have an elevated blood pressure of 180/100 mmHg and she was given 25 mg IV Lasix treatment Her oxygen saturation was normal, and heart rate was elevated to 140 bpm. On physical exam it was noted that she had mild pain on deep palpation in the epigastric region and the left hypochondrium region. On extension day 150 a head CT showed atrophic enlargement of the ventricular system and periventricular white matter hypodensity. Three hours after the CT her blood pressure was elevated again to 180/75 mmHg and she received Lasix 25 mg. About 6 hours later she was found unresponsive to verbal stimuli and painful stimuli with a blood pressure of 80/60 mmHg, and an oxygen saturation of 76%. Repeat CT did not show a new lesion compared to the initial CT. She died later the same day due to cardiorespiratory arrest with a suspected cerebral vascular accident. No autopsy was performed.

Reviewer Comment: In this case there was insufficient information to make a causality determination. This subject had received lecanemab during the Core, so was not a new exposure to study drug, unlike the other subjects described above, and did not have an ApoE e4 allele which increases risk of ARIA. Her presentation was also confounded by the presence of gastrointestinal symptoms and lack of an MRI to determine if she indeed had a cerebrovascular accident or ARIA-E or ARIA-H.

Description of Deaths in Study 201 OLE

As of data cutoff day of December 1, 2022, there have been no changes to the number of deaths in 201 OLE since the review of the original BLA761269 submission. As stated earlier there were 5 deaths ((b) (6)) out of 180 subjects in Study 201 OLE (incidence of 2.8 %). All but two ((b) (6)) of these

deaths occurred within 30 days of the last dose of study administration. Two deaths ((b) (6)) occurred after 30 days of study drug administration. These have been reviewed at the time of the original submission and will not be discussed further.

The preferred terms of adverse events with fatal outcomes for deaths during the 201 OLE period are provided in Table 9. Overall based on the previous review of these death narratives as part of the original BLA761269 safety review, I could not identify a role of the study drug in any of these deaths. Narratives are provided in the original safety review.

Table 9 Deaths in Lecanemab-Treated Subjects in Study 201 OLE

Subject ID	Age, Race, Sex	Dose (mg/kg)	AE listed as cause of death	Risk Factors
(b) (6) Treatment emergent	80-year-old white female	LEC10-BW	Cervical vertebral fracture	Car accident
(b) (6) Not Treatment emergent	76-year-old white female	LEC10-BW	COVID-19 pneumonia	COVID Epidemic, age
(b) (6) Not treatment emergent	82-year-old white female	LEC10-BW	Alzheimer's type dementia	Alzheimer's disease, age
(b) (6) Treatment emergent	79-year-old white male	LEC10-BW	Metastatic malignant neoplasm of brain	Presence of malignancy (metastatic lung cancer)
(b) (6) Treatment emergent	76-year-old white male	LEC10-BW	Metastatic Neuroendocrine carcinoma	Diabetes Mellitus

Description of Deaths in the ongoing 301 Core Study in China
As of December 1, 2022, in the ongoing 301 Core study in China, there has been one death ((b) (6)) due to nonvalvular and paroxysmal atrial fibrillation. Because the study drug is blinded, the narrative of this subject will not be included in this review.

Description of Deaths in the Ongoing Study 303
Neither Study A3 or Study A45 had any deaths reported due to ARIA-E, ARIA-H, skin rash or other hypersensitivity reaction as of the data cut off of December 1, 2022.

7.4.2. Serious Adverse Events

In the placebo-controlled Study 301 Core, treatment emergent serious adverse events (SAEs) occurred in 14% (126/898) of lecanemab-treated subjects and in 11% (101/897) of placebo-treated subjects . The primary organ class (POC) categories with the highest incidence of SAEs in the lecanemab arm and greater than placebo were Injury, poisoning and procedural

complications (3%, driven by infusion reactions) and Nervous system disorders (3%, driven by ARIA-E and syncope), followed by Cardiac disorders (2%) and Infections and infestations (2%).

The most frequently reported SAEs in 2 or more subjects receiving lecanemab and greater than placebo were infusion related reactions (1.2% vs 0), ARIA-E (0.8% vs 0), atrial fibrillation (0.7 vs 0.3 %), angina pectoris (0.7% vs 0), and syncope (0.7% vs 0.1 %) (Table 10). ARIA and infusion-related reactions will be discussed in more detail as adverse events of special interest (Section 7.5.1 and Section 7.5.3). Selected narratives can be found in Appendix Section 12.1.4.)

Table 10 Incidence of Treatment Emergent SAEs in 301 Core by Preferred Term Occurring in 2 or More Subjects on Lecanemab and at Higher Frequency Compared to Placebo

MedDRA System Organ Class* MedDRA Preferred Term	Placebo N=897 n (%)	Lecanemab N=898 n (%)
Injury, poisoning and procedural complications	**19(2.1)**	**31(3.4)**
Infusion related reaction	0	11 (1.2)
Fracture**	12(1.3)	13(1.4)
Fall	1 (0.1)	3 (0.3)
Nervous system disorders	**15(1.7)**	**30(3.3)**
Amyloid related imaging abnormality-edema/effusion (ARIA-E)	0	7 (0.8)
Syncope	2 (0.2)	6(0.7)
Amyloid related imaging abnormality-microhemorrhages and hemosiderin deposits (ARIA-H)	0	2 (0.3)
Cerebral hemorrhage > 1 cm	0	3(0.3)
Cardiac disorders	**9(1)**	**19(2.1)**
Atrial fibrillation	3 (0.3)	6 (0.7)
Angina pectoris	0	6(0.7)
Acute myocardial infarction	0	2 (0.3)
Coronary artery disease	0	2 (0.3)
Infections and infestations	**9(1)**	**19(2)**
Diverticulitis	1 (0.1)	4(0.4)
COVID-19 pneumonia/COVID 19	2 (0.2)	4 (0.4)
Cellulitis	0	2 (0.3)
Renal and Urinary Disorders	**4(0.4)**	**5(0.6)**
Acute kidney injury	0	2 (0.3)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**16(1.8)**	**17(1.9)**
Invasive ductal breast carcinoma	0	2 (0.3)
Diarrhea	0	2 (0.3)
Respiratory, thoracic and mediastinal disorders	**6(0.7)**	**9(1)**
Pulmonary edema	0	2 (0.3)
Respiratory failure	0	2 (0.3)
General Disorders and administration site conditions	**2(0.2)**	**6(0.7)**

MedDRA System Organ Class* MedDRA Preferred Term	Placebo N=897 n (%)	Lecanemab N=898 n (%)
Non-cardiac chest pain	0	4 (0.4)
Metabolism and Nutrition Disorders	**2(0.2)**	**5(0.6)**
Hyponatremia	0	2 (0.3)

Reviewer Created using the ADAE dataset.
**Under the System Organ Class heading the numbers represent any subject who had one or more TEAE falling under that classification. Only preferred terms occurring under a SOC in 2 or more subjects on lecanemab and at higher frequency compared to placebo are listed.*
*** Includes the following PTs: on lecanemab: thoracic vertebral fracture (n=2), patellar fracture (1), rib fracture (1), upper limb fracture (1), wrist fracture(1), on placebo (spinal compression fracture (1), (upper limb fracture=1).*
Two subjects who had an SAE of ARIA-H microhemorrhage, also had an SAE of ARIA-E

301 OLE

The incidence of SAEs in the ongoing OLE period as of December 1, 2022, was 9.1% (126/1385). The most common SAEs were ARIA-E (0.8%, 11/1385), infusion related reactions 0.7% (10/1395), fracture 0.6% (8/1385) and ARIA-H (0.5%, 7/1385). See Appendix Section 12.1.4 Table 37.

In terms of SAEs of special interest, as of data cutoff of December 1, 2022, there were seven serious ARIA-E events (two with serious ARIA-H events), during the 301 Core, and 14 ARIA related SAEs in 301 OLE.(Table 35) Additionally there were a total of 7 SAEs of cerebral hemorrhage > 1 cm in lecanemab treated subjects in the 301 Core and OLE combined , most ((b) (6)) occurring within 30 days of a dose, and (b) (6) occurring within 40 days after the last dose of study drug in the setting of worsening ARIA that began within 30 days of a dose. See Section 12.1.9 for ARIA and Cerebral Hemorrhage and related narratives. There were 20 SAEs of infusion related reactions in lecanemab exposed subjects in 301 Core and OLE combined, and 2 subjects with hypersensitivity (Section 12.1.10 Table 83). Most occurred after the first infusion.

Potentially Medically Significant SAEs

I did not identify any SAEs of acute pancreatitis, blind, ischemic colitis, congenital anomalies, disseminated intravascular coagulation endotoxic shock, confirmed or suspected, hemolysis, hemolytic anemia, liver necrosis, liver transplant, neuroleptic malignant syndrome, progressive multifocal leukoencephalopathy, product infectious disease transmission, pulmonary fibrosis, pulmonary hypertension, serotonin syndrome, Stevens-Johnson syndrome, Torsade de Pointes, toxic epidermal necrolysis, thrombotic thrombocytopenic purpura, and ventricular fibrillation.

In 301 Core and OLE I identified SAEs of the following designated medical events in subjects receiving lecanemab: acute respiratory failure/respiratory failure (b) (6)), rhabdomyolysis (b) (6)), motor neuron disease (b) (6)), and acute kidney injury, (b) (6)). I did not identify a clear role for lecanemab in most of these cases, due to the presence of other factors such as past medical history, concomitant medications, or other concomitant medical events at the time of the SAEs. Subject (b) (6) had acute interstitial

nephritis, which is usually drug induced, but also was on allopurinol which has also been associated with interstitial nephritis. Events of seizure and of suicidality will be discussed in Sections 7.5.5 and 7.5.6, respectively. One subject experienced severe infusion related reaction which was described as an anaphylactic reaction. See Section 7.5.3 for a description of this subject.

201 OLE

As of data cut off of December 1, 2022, the overall incidence of treatment emergent SAEs in the ongoing 201 OLE study was 50/180 (29 %) (Table 49) (compared to 25% at the time of the April 15, 2022, data cut-off date. There were few new SAEs: one cervical fracture, three falls, one cerebrovascular infarct, 2 new COVID-19 cases. See Section 12.1.5 for descriptions of SAEs in 201 OLE. There were no new safety signals in the 201 OLE 90-day updated SAE data.

Please see Section 12.1.5 for SAEs in ongoing blinded studies including 301 Core in China, and 303 studies.

Medical Officer's Assessment: SAEs reported in Study 301 Core and OLE and ongoing 201 OLE were consistent with those reported in the original submission

7.4.3. Discontinuations Due to Adverse Effects

In 301 Core, 22% of subjects receiving the study drug discontinued study treatment compared to 17% on placebo (Table 38). Study discontinuation due to adverse events occurred in 54/898 (6%) on lecanemab, and 30/897 (3%) subjects on placebo. Discontinuations on lecanemab were driven by ARIA and by infusion related reactions. During the 301 Core discontinuations from study treatment due to adverse events occurred in 7% of subjects receiving study drug compared to 3 % on placebo. Detailed reasons for treatment discontinuation and study withdrawal are shown in section 12.1.6. Of note, discontinuation of study drug was mandated in the protocol for the following reasons:

- infusion or injection reactions associated with administration of study drug of Grade 3 severity or above that do not lessen or resolve with treatment
- clinical features indicating meningoencephalitis
- hypersensitivity reactions with clinical features of tissue injury
- severe ARIA-E associated with SAE
- subjects with ARIA-H and ARIA-E that resulted in study drug interruption at any point during the course of the study will permanently discontinue study drug if a 3rd occurrence of either event (i.e., ARIA-H or ARIA-E) meets the criteria for study drug interruption or discontinuation.

In the 301 Core study, the most frequently reported TEAEs leading to treatment discontinuation by primary organ system were: nervous system disorders, and injury, poisoning and procedural complications. (Table 11).

Table 11 TEAEs leading to Study Drug Discontinuation in 301 Core in > 1 Subject Receiving Lecanemab and at Greater Frequency than Placebo by Study Arm and Primary Organ System

System Organ Class	Placebo N=897 n (%)	Lecanemab N=898 n (%)
Nervous system disorders	8(0.9)	29(3.2)
Injury, poisoning and procedural complications	5(0.6)	13(1.4)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	3(0.3)	6(0.7)
Psychiatric disorders	1(0.1)	3(0.3)
General disorders and administration site conditions	1(0.1)	2(0.2)
Skin and subcutaneous tissue disorders	1(0.1)	2(0.2)
Blood and lymphatic system disorders	0	1(0.1)
Hepatobiliary disorders	0	1(0.1)
Metabolism and nutrition disorders	0	1(0.1)
Renal and urinary disorders	0	1(0.1)

Safety population and TRTEMFL = Y
[teaediscon1.rtf] [teaediscon1.sas] 20APR2023, 08:5

In the placebo-controlled period of Study 301, most frequently reported TEAEs leading to treatment discontinuation in order of frequency, were ARIA-H microhemorrhage, ARIA-E, infusion related reactions and superficial siderosis (Table 12). The following TEAEs of interest resulted in study drug discontinuation in 1 lecanemab subject each in 301 Core: subdural hematoma, cerebral hemorrhage, hypersensitivity, and urticaria.

Table 12 TEAEs leading to Study Drug Discontinuation in > 1 Subject Receiving Lecanemab and at Greater Frequency than Placebo by Study Arm and Dictionary Derived Term in 301 Core

Dictionary-Derived Term	Placebo N=897 n (%)	Lecanemab N=898 n (%)
Amyloid related imaging abnormality-microhemorrhages and hemosiderin deposits	1(0.1)	15 (1.7)
Amyloid related imaging abnormality-oedema/effusion	0	14(1.6)
Infusion related reaction	1(0.1)	12 (1.3)
Superficial siderosis of central nervous system	0	4 (0.5)
Depression	0	2 (0.2)

Safety population and TRTEMFL = Y, [teaediscon1.rtf] [teaediscon1.sas] 20APR2023, 08:5

Narratives of discontinuations by dictionary derived term that occurred in at least 2 subjects in the LEC arm and at higher frequency compared to placebo are included in Section 12.1.6.

301 OLE:

In 301 OLE period alone, 4.1% (57/1385) of patients discontinued lecanemab due to adverse events (Table 39). The most common reasons for study drug discontinuations during the 301 OLE were similar to the 301 Core phase and included, ARIA-E, ARIA-H and infusion-related

reactions. In addition the following TEAEs of interest leading to discontinuation occurring in 1-3 person are also noted and will be discussed in Section 12.1.6: cerebral hemorrhage (n=3), superficial siderosis (n=3), hypersensitivity(1), rash(1), and brain neoplasm (1). See Section 12.1.6 Table 39 for PTs leading to study discontinuation and occurring in more than 3 subjects. In the lecanemab treated subjects as a whole, when combining the Core and OLE period, the incidence of study drug discontinuation due to AEs was 8% (124 out of 1612), most common TEAES that led to study drug discontinuation were similar to 301 Core and 301 OLE alone.

201 OLE
There was only one new AE leading to discontinuation in 201 OLE since the original review. This was due to COVID-19 pneumonia and did not appear to be study drug related. See Section 12.1.6 for more details related to discontinuations in Study 201 OLE.

Other ongoing Studies
A listing of AEs leading to discontinuation in the 301 OLE, 201 OLE, and blinded studies 301 (China) and 303, and selected narratives are available in Appendix Section 12.1.6.

Reviewer's Comment: ARIA-E, ARIA-H, and infusion related reactions were the leading adverse events associated with discontinuation of lecanemab. These findings are consistent with those associated with discontinuation in the original lecanemab BLA, with no new patterns of concern.

7.4.4. Significant Adverse Events

Overall, the evaluation of significant AEs did not identify a new safety signal. Most TEAEs were mild or moderate, with approximately 7 % considered severe in both the lecanemab and placebo arms. (Table 13)Similarly, during the 301 OLE period 5% of subjects had a severe TEAE.

In Study 301 Core, the preferred terms for the severe AEs with the highest frequency on lecanemab vs placebo were infusion related reaction (0.8% vs 0), fall (0.4% vs 0.2%), and ARIA-E (0.3% vs 0). During the OLE the most frequent severe TEAEs were ARIA-E (0.7%), and infusion related reactions (0.5%).

Table 13 Incidence of a Subject Experiencing a TEAE by Maximum Severity in Study 301- Core

	Placebo N= 897 n (%)	LEC10-BW N =898 n (%)
Mild	388(43.3)	396(44.1)
Moderate	288(32.1)	337(37.5)
Severe	61(6.8)	67(7.5)

Reviewer created by the reviewer using 301 ADAE,; SAFFL=Y; TRTEMFL=Y; selection of worst severity rating for each subject, Grouped by USUBJID, Severity/Intensity, Actual Treatment in Period01; Tabulate by Severity and Actual Treatment in Period 1 (Reassigned order of dose)

In the placebo-controlled period of Study 301, the most frequent severe TEAEs were Infusion related reactions, falls and ARIA-E Table 14. The TEAE severity rating was based on the clinical judgement of the investigator based on the functional impact of the TEAE. The TEAE severity rating did not always match the radiographic severity rating of an ARIA event.

Table 14 Incidence of Severe TEAEs Occurring in ≥ 2 Subjects on Lecanemab and at Higher Incidence Compared to Placebo in 301 Core

	Placebo N= 897 n (%)	LEC10-BW N =898 n (%)
Total Subjects with Any Severe Adverse Event	61 (6.8)	67 (7.5)
Infusion related reaction	0	7(0.8)
Fall	2(0.2)	4(0.4)
Amyloid related imaging abnormality-oedema/effusion	0	3(0.3)
Hip fracture	1(0.1)	3(0.3)
Pulmonary edema	0	2(0.2)

Safety population and TRTEMFL = Y [teaesev1.rtf] [teaesev1.sas] 15MAY2023, 15
Clinical Analyst Created:40

Severity of TEAEs in 301 OLE was similar to that observed during the Core (see Appendix Section 12.1.7, Table 50 Treatment Emergent Severe Adverse Events in 301 OLE Occurring in 2 or More Subjects.). During the 301 OLE, 46% of subjects had a mild TEAE, 23% moderate and 5% severe. The most frequent severe TEAEs in 301 OLE were ARIA-E (0.7%, 9/1385), infusion related reactions (0.5%, 7/1385), and cerebrovascular accident (0.3%, 4/1385).

7.4.5. Treatment Emergent Adverse Events and Adverse Reactions

Study 301 Core is the primary source of data used to assess the treatment emergent adverse reactions (TEAE) for lecanemab in this sBLA and will be presented in product labeling.

Results of the FDA analysis of TEAEs from 301 Core are shown in Table 15. The incidence of TEAEs in 301 Core was 89% in the lecanemab arm and 82% in the placebo arm. The most common TEAEs by primary organ system occurring at a higher incidence in lecanemab vs placebo were Nervous System Disorders (44% vs 32%), Injury, Poisoning and Procedural Complications (41 % vs 28 %), and Infections and infestations (36% vs 32%). A complete list by organ system can be found in Appendix Section 13.1.1 Table 43 .

The most common TEAEs occurring in at least 5% of subjects in the lecanemab arm compared to placebo in 301 Core were infusion related reactions, ARIA-H, ARIA-E and headache, all already established during the initial review and currently listed in the Leqembi label. Of note, some similar TEAE terms have been pooled to detect a signal that would not otherwise be seen if similar terms were evaluated individually.

Table 15 Incidence of TEAEs by Preferred Term and Medical Query Group occurring ≥ 5% on Lecanemab and ≥2% Greater than Placebo in 301 Core

Dictionary Derived Term	Placebo N= 897 n (%)	LEC10-BW N =898 n (%)
Infusion related reaction	64 (7.1)	236 (26.3)
Amyloid related imaging abnormality-microhemorrhages	69 (7.7)	126 (14.0)
Amyloid related imaging abnormality-edema/effusion	15 (1.7)	113 (12.6)
Headache	73 (8.1)	101 (11.2)
Rash MQG[1] -	37 (4.1)	52 (5.8)
Superficial siderosis of central nervous system	22 (2.5)	50 (5.6)
Nausea and Vomiting	37 (4)	50 (6)

Safety population and TRTEMFL = Y, [teae1.rtf] [teae1.sas] 12APR2023, 12:20
Clinical Analyst Created
MQG: Medical Query Group
[1]Rash MQG includes the following preferred terms: acne, dermatitis, erythema, erythema migrans, infusion site rash, injection site rash, pemphigo, rash, rash erythematous, rash macular, rash maculopapular, rash popular, rash pruritic, skin exfoliations, skin irritation, skin reactions, and urticaria. See Section 12.1.7.1 Table 44 for a table including all PTs included under this MQG by treatment arm.
Subject (b) (6) who had ARIA-H microhemorrhage was counted in the table of TEAEs but not under ARIA tables, because this event was not captured under the AE of Special Interest, because the investigator determined that the ARIA-H in this subject was due to a head injury.

The following less common ADRs in Study 301 Core identified during the review process with incidence in the lecanemab vs placebo arms provided in parenthesis include: hypersensitivity (1.7% vs 0.9%), lip swelling (0.1% vs 0), urticaria (0.6% vs 0.3%), atrial fibrillation/atrial flutter (2.8% vs 1.6%), pyrexia (2.7% vs 2%).

Additionally, three FDA-created MQGs identified through the MQG analysis which were not included in Table 15 will be discussed further.

Infection all MQG occurred in 26% on placebo and 30% on lecanemab. The following preferred terms (PTs) occurred in 3 or more subjects on the lecanemab arm vs placebo: bronchitis (1.3% vs 0.5%), cellulitis (1.2% vs 0.8), cystitis (1% vs 0.3%), gastroenteritis (1% vs 0.6%), influenza (0.6% vs 0.1%), pharyngitis (0.7% vs 0.2%), tooth abscess (1% vs 0.6%), upper respiratory tract infection (2.9% vs 2.1%), and viral infection (0.6% vs 0). The significance of this finding is unclear.

The arrythmia FDA N grouping occurred in 5.2% for lecanemab vs 3.5% for placebo. The following PTs occurred in three or more subjects receiving lecanemab vs placebo (with % incidence in placebo vs lecanemab arm provided in parenthesis): arrhythmia (0.3% vs 0), atrial fibrillation and atrial flutter (2.8% vs 1.6%), sinus bradycardia (0.8% vs 0.3%), and ventricular extrasystole (0.7% vs 0.3%). The difference seems to be mainly driven by a higher incidence of

atrial fibrillation or atrial flutter in the lecanemab arm compared to placebo. The imbalance in atrial fibrillation was also seen during the 201 Core study where atrial fibrillation occurred in 4% subjects receiving study drug compared to 1% receiving placebo.

Hemorrhage FDA N was mainly driven by hematuria that occurred in 2.3% on lecanemab vs 0.8% on placebo and will be further discussed under Section 7.4.6.

One of the most common symptoms of ARIA is headache. In 301 Core, headache was observed in 12 out of 25 subjects on lecanemab with symptomatic ARIA-E, of which 2 had ARIA-E and ARIA-H microhemorrhage associated with headache, and one had ARIA-E and superficial siderosis associated with headache. There were 2 headaches associated with isolated ARIA-H microhemorrhage, and one with isolated cerebral hemorrhage. When I analyzed the incidence of headache, excluding subjects who had ARIA or cerebral hemorrhage any time during the 301 Core study, 10% (73/705) of those on lecanemab and 8% (68/812) on placebo (compared to 11% (101/898) on lecanemab versus 8% (73/897) on placebo inclusive of those with ARIA and cerebral hemorrhage) had a headache.

Please see Section 12.1.4 for further discussion related to TEAEs of Designated Medical Events.

There were 1% (9/898) of subjects on lecanemab and 0.6% (5/897) on placebo in 301 Core had a PT of acute kidney injury or renal failure. Of the 9 subjects on lecanemab, two were serious ((b) (6)), none were serious on placebo. These cases are described under Section 7.4.2 and also Section 12.1.4.The remaining 7 subjects had a TEAE of acute kidney injury that was not serious; these subjects did not have narratives. Severity rating was moderate for 2/7 ((b) (6)) and mild in five subjects ((b) (6) . Outcome was not resolved in three subjects (b) (6)), and resolved in the remaining subjects. Investigator causality was yes for one subject (b) (6) , and no for the rest of these subjects. Based on my review of subject (b) (6) , I also could not rule out a role of study drug in this case (see Section 7.4.2).

TEAEs occurred in 74% (1020/1385) of patients in 301 OLE. In 301 OLE, the most common (≥5%) TEAEs were infusion related reactions (13%), COVID-19 (13%), ARIA-H microhemorrhages (12%), ARIA-E (8%), headache (6%), and fall (6%). (Section 12.1.7 Table 45) The lower incidence of infusion related reaction, ARIA-E and ARIA-H during the 301 OLE period, compared to 301 Core in lecanemab treated subjects likely reflects that close to half of the patients in the 301 OLE period had already been exposed to lecanemab up to 18 months.

Study 201 OLE
Study 201 OLE Phase the most common (>10%) TEAEs were: fall (24.4%), infusion-related reaction (21.1%), urinary tract infection (15.6%), COVID-19 (13.9%), ARIA-H microhemorrhage (13.3%), arthralgia 10.6%), and nasopharyngitis (10.6%) (Table 51)

7.4.6. Laboratory Findings

During the original submission, the main finding related to laboratory assessments in Study 201 Core was that those receiving lecanemab were more likely to experience a transient decrease in lymphocytes, and an increase in neutrophils after the first infusion. Because in 301 Core blood collection only occurred prior to the infusion whether there is a reduction in lymphocyte count and increase in neutrophils immediately after an infusion could not be assessed with this supplemental submission. In Study 301 Core, blood collection for laboratory assessments occurred at week 1,3, 7,13,27,39, 53, 65, 79, early termination visit, 3-month follow up visit or unscheduled visits as needed.

In Study 301 Core, there were no clear trends or differences in hematology, or chemistry values between the placebo and lecanemab groups. Because of difficulty of interpreting the significance of laboratory values without a comparator group, laboratory safety analysis focused on 301 Core data.

For the analysis of laboratory findings, I reviewed the mean and mean change from baseline by visit, shifts to one or more abnormal value as defined by the FDA at any point post-baseline, inclusive of unscheduled visits, as well as the last assessment during 301 Core. I also reviewed TEAEs related to abnormal laboratory findings.

Hematology

Examination of the number of subjects with one or more hematology value with abnormal values meeting FDA- specified abnormal levels at any point post-baseline, did not identify any significant differences between lecanemab vs placebo (See Appendix Section 12.1.11 Table 85). Similarly at the end of the study, which is the last record of each subject including unscheduled, or early termination visits, there were no differences in hematology values between Core and placebo. (See Appendix Section 12.1.4, Table 86).

Evaluation of mean hematology values and changes from baseline at each visit also did not identify any notable differences between lecanemab and placebo overall.

Chemistry

Examination of the number of subjects with one or more chemistry with abnormal values meeting FDA- specified levels at any point post-baseline, did not identify any significant differences between lecanemab vs placebo (See Appendix Section 12.1.4 Table 87). Similarly at the end of the study, which is the last record of each subject including unscheduled, or early termination visits there were no notable differences in chemistry values between Core and placebo. (See Appendix Section 12.1.4 Table 88).

Evaluation of mean chemistry values and changes from baseline at each visit, also did not identify any significant differences between lecanemab and placebo.

Hepatic-Related Events

I did not identify a safety signal for hepatic related events on treatment in an analysis of maximum post baseline and end of study liver enzyme values, hepatic related adverse events in Study 301 Core (Appendix Section 12.1.4, Table 91). There was one Hy's Law case (b) (6) in Study 301 Core who was on placebo. No Hy's Law cases were found after exposure to lecanemab based on alanine transaminase (ALT) or aspartate transaminase) AST ≥ 3ULN and bilirubin (BIL) ≥ 2 ULN within 30 days of ALT/AST elevation in 301 Core and OLE period (Section 12.1.4 Table 92).

TEAEs of abnormal laboratory results

In my review of TEAEs belonging to the system organ classes (SOC) Investigations related to laboratory findings, LEC10-BW did not have an excess of laboratory related TEAEs compared to placebo in Study 301 Core (incidence of 6.5% versus 6.2%, respectively).

When examining the laboratory related TEAEs in 301 Core, some of the findings from the 201 Core were not observed in 301 Core: TEAEs of lymphopenia/lymphocyte reduced, glycosuria, or glucose urine present, hyperglycemia or blood glucose increased, neutrophil count increased were observed at higher frequency on lecanemab during 201 Core, but this was not observed in 301 Core.

The laboratory related TEAE which had the highest difference between lecanemab and placebo was hematuria. Similar to observations in 201 Core, there was a higher incidence of hematuria on lecanemab 2.3% (21/898) vs 0.7% (7/898) on placebo. While the following laboratory related TEAEs occurred in 2 or more subjects on lecanemab compared to placebo, the overall numbers were too small to draw any conclusions: hypokalemia, neutropenia, hyponatremia, hypothyroidism, vitamin D deficiency/vitamin D decreased, proteinuria, hypoglycemia, blood calcium decreased, and blood phosphorus decreased.

There were 21 lecanemab treated subjects and 8 placebo subjects who experienced hematuria or blood urine present. None were serious events. None were deemed to be study drug related by the investigator.

In the majority of subjects on lecanemab with hematuria, either there was no narrative, or the narrative was for another event and did not include a description of events leading to hematuria. There were two subjects that had a narrative describing hematuria, in one (b) (6)) hematuria was due to ongoing renal cyst and renal failure, with a superimposed fall and flank injury. In subject (b) (6) hematuria was due to an enlarged prostate and nephrolithiasis. In neither of these cases, it appeared that the drug played a role in hematuria. In one subject (b) (6)), while hematuria was not described, the narrative described

rhinorrhea on study day 4 after the first dose of study drug which was described as a hypersensitivity reaction. The hematuria occurred 2.5 months after the rhinorrhea in the setting of urinary retention. Thus, it seems more likely that the hematuria may be related to the event that led to urinary retention rather than represent a hypersensitivity reaction.

Reviewer Comment: There is insufficient data to determine if hematuria was related to study drug in these subjects.

Urine analysis

I reviewed the Applicant's Tables 14.3.4.3.3.3 Abnormal Laboratory Post-Baseline with Normal Baseline-Laboratory Urinalysis results (urine pH and Specific Gravity), 14.3.4.3.2.1 Laboratory Urinalysis Results (pH, specific gravity, urobilinogen) -shifts from Baseline to postbaseline visits, and 14.3.4.3.2.2 Laboratory urinalysis results (pH, urobilinogen, pH) shifts from baseline to postbaseline visits for lab parameters with normal and abnormal classification. I could not identify any trends to suggest differences between lecanemab and placebo arms.

I also reviewed shifts from baseline to any postbaseline visit with > 5 red blood cells (RBC) per high power field (HPF). Regardless of baseline status (>5 RBC/ HPF or < 5 RBC/ HPF), shifts to >5 RBC /HPF was not different between placebo and lecanemab.

7.4.7. Vital Signs

For Study 301 Core, I reviewed the number of subjects with one or more abnormal vital signs any time during the study, as well as the mean values by visit including pre and post infusion.

When examining the mean values by visit pre and post infusion, I did not identify any trends in the mean values for vital signs that were different between lecanemab and placebo.
When examining the minimum and maximum values at each visit pre and post infusion, the maximum temperature for some post-infusion visits was elevated to 38 -39° C on lecanemab. However, this was also observed in some subjects on placebo post infusion visits as well.

When examining shifts from baseline to abnormal vital signs, the following appeared to have occurred at ≥ 2% frequency on lecanemab compared to placebo: pulse rate >100, respiratory rate <12, respiratory rate >20, weight decrease ≥7% from baseline (Table 16) The significance of these findings is not clear.

Table 16 Abnormal Vital Signs at Any Postbaseline Time Point in 301 Core

Criteria	Placebo (N = 897) n (%)	Lecanemab 10mg/bi-weekly (N = 898) n (%)
DBP <50 mmHg	67 (7.5)	67 (7.5)

Criteria	Placebo (N = 897) n (%)	Lecanemab 10mg/bi-weekly (N = 898) n (%)
DBP > 90 mmHg	271 (30.2)	263 (29.3)
DBP >100 mmHg	21 (2.3)	29 (3.2)
Pulse rate <60 bpm	512 (57.1)	489 (54.5)
Pulse rate >100 bpm	21 (2.3)	37 (4.1)
Respiratory rate <12 breaths/min	56 (6.2)	82 (9.1)
Respiratory rate >20 breaths/min	85 (9.5)	115 (12.8)
SBP <90 mmHg	23 (2.6)	32 (3.6)
SBP >140 mmHg	502 (56.0)	498 (55.5)
SBP >160 mmHg	119 (13.3)	113 (12.6)
Temperature <36.0 C	358 (39.9)	339 (37.8)
Temperature >38.0 C	13 (1.4)	16 (1.8)
Weight decrease ≥7 % from baseline	128 (14.3)	147 (16.4)
Weight increase ≥7 % from baseline	140 (15.6)	125 (13.9)

Safety population and including any post baseline during DB period
[tvsabn1.rtf] [tvsabn1.sas] 12APR2023, 12:20

I also examined the Applicant's table 14.3.4.5.3.2 which included abnormal vital signs post baseline with normal baseline. The findings were similar to that of Table 16 above, and the following showed a ≥ 2% frequency difference (higher on lecanemab) between the placebo vs lecanemab arms: systolic blood pressure < 90 mmHg (3 % vs 4.5%), pulse rate > 100 beats/min (2.9% vs 5.5%), weight decrease of ≥7% from baseline (13.7% vs 15.9%), and respiratory rate < 12 breaths/min (5.8% vs 8.7%) and > 20 breaths/min (9.1% vs 13.1%)

When I examined the TEAEs under the Primary Organ System Investigations related to vital signs in the 301 Core Study, I did not identify any TEAEs that occurred in the LEC10-BW arm at an incidence of 2% or higher compared to placebo; there was not a higher incidence of 2% or higher in TEAEs of bradycardia, hypotension, hypertension, syncope, or orthostatic hypotension on the lecanemab arm compared to placebo.

7.4.8. Electrocardiograms (ECGs)

Overall, I did not identify a clinically meaningful difference in changes in ECG measures during the course of 301 Core in subjects on lecanemab compared to placebo.

During Study 301 Core, ECGs were obtained on week 9, 17, 27, 39, 53, 65, 79, early termination visit, 3 month follow up visit and unscheduled visits as needed.

I reviewed mean and mean change from baseline by visit in 301 Core study which include the following values: heart rate, PR interval, QRS duration, QT interval, QTc Interval, QTcFAG (QTcF aggregate), RR interval, Overall, there was no consistent trend of worsening in any of these ECG parameters in subjects on lecanemab compared to placebo.

I reviewed ECG shifts from baseline to one or more abnormal clinical assessments. There was not a higher incidence of shifts from normal baseline, abnormal not clinically significant (NCS) baseline, and abnormal clinically significant (CS) baseline to normal or abnormal NCS in the lecanemab arm compared to placebo. (See Section 13.1.3, Table 83).

I also reviewed sponsor table 14.3.4.6.2, ECG shifts from baseline to postbaseline visits, by visit, and did not identify any consistent trends of higher incidence of abnormal NCS or abnormal CS in the lecanemab arm compared to placebo.

According to sponsor Table 14.3.4.6.3, the incidence of having at least one QTcF postbaseline increase from baseline of > 30ms, > 60 ms, at least one postbaseline value of > 450ms, > 480msec, > 500msec and >450 msec combined with increase from baseline of > 60 sec was consistently slightly higher on the lecanemab arm. The difference between the incidence between lecanemab and placebo ranged from 0.1% to 1.2%, thus the clinical significance of these findings is unclear.

The following TEAEs related to ECG findings were identified in Study 301 Core (Table 17). The only notable difference between placebo and lecanemab was in the number of subjects with QT prolongation. See Section 7.4.9 for a more detailed discussion of QT prolongation.

Table 17 Incidence of TEAEs Related to ECG Abnormalities in 301 Core

Preferred Term	Placebo N=897 n (%)	Lecanemab N=898 n (%)
Electrocardiogram QT prolonged	0	6 (0.7)
Electrocardiogram T wave inversion	4(0.5)	3(0.3)
Electrocardiogram PR prolongation	0	2 (0.2)
Electrocardiogram abnormal	0	1(0.1)
Electrocardiogram ST segment depression	1(0.1)	1(0.1)
Electrocardiogram T wave abnormal	0	1(0.1)
Electrocardiogram T wave amplitude decreased	1(0.1)	1(0.1)
Electrocardiogram ST segment elevation	1(0.1)	0

Reviewer created using adae.xpt.

7.4.9.QT

A TEAE of with a preferred term of Electrocardiogram QT Prolonged while on lecanemab, occurred in 6 subjects on lecanemab and 0 subjects on placebo. The onset of QT prolongation was in the range of after the 5th -34th dose of study drug. Of the 6 subjects who had QT prolongation while on lecanemab, all events were rated as mild in severity, and only one (b) (6)) was serious, thus there was no narrative for 5 of the 6 events. Subject (b) (6) is an 83-year-old man with past medical history of hypercholesterolemia. On study day 353, after having 25 doses of study drug, the subject experienced dizziness and profuse sweating, and in the ER was found to have left ventricular failure, QT prolongation, first degree AV block and sinus bradycardia. No action was taken with study drug. He was treated with lisinopril. The AV block and bradycardia resolved, and QT prolongation and left ventricular failure was ongoing. The subject had the last dose of study drug on study day 539 and completed 301 Core and entered the 301 OLE. Investigator assigned causality was yes for one ((b) (6)) out of 6 events. In this subject's case there were no other cardiac related TEAEs listed in the ADAE dataset. There was one other subject (b) (6)), who did not have any other cardiac related TEAEs listed. Subject (b) (6) had two TEAEs of palpitations, subject (b) (6) had a TEAE of dizziness, and subject (b) (6) also had TEAEs of bradycardia and arrhythmia. Given the limited information, I am unable to ascertain whether study drug played a role in these events of QT prolongation. There was no action taken with study drug as a result of these events, dose was not changed, interrupted or discontinued due to this TEAE.

In 301 OLE there was one subject who had a TEAE of QT prolongation (b) (6)), this was not a serious event, and occurred after the 66th dose of lecanemab in this subject.

In accordance with ICH E14 guidelines for monoclonal antibodies that have a low likelihood of direct ion channel interactions, a dedicated QT study was not conducted.

7.4.10. Immunogenicity

In Study 201 Core, limitations of the antidrug antibody (ADA) assay precluded definitive conclusions regarding the impact of ADA on lecanemab safety. As noted in the original review, the plasma concentrations of lecanemab in 201 Core exceeded the drug tolerance level of the ADA and Nab assays. In that case, the presence of lecanemab in the sample interferes with the ADA assay, so that a negative result of an ADA sample is considered inconclusive, and this may result in an underestimation of ADA and Nab positivity. Postmarketing requirements (4384-2 and 4384-3) were imposed with the January 6, 2023, accelerated approval, to improve the assay sensitivity and to use the improved and validated assay to assess the impact of antibody formation on pharmacokinetics, pharmacodynamics, safety, and efficacy of lecanemab in patients enrolled in the confirmatory study. In their review of S-001, OCP and OPB concluded that the assay remains inadequate for this purpose. The impact of immunogenicity on pharmacokinetics, pharmacodynamics, efficacy, and safety will be evaluated when data to support the postmarketing requirements (PMRs) are submitted.

7.5. Analysis of Submission-Specific Safety Issues

7.5.1. ARIA

Monoclonal antibodies directed against aggregated forms of beta amyloid, including lecanemab, can cause amyloid related imaging abnormalities (ARIA) characterized as ARIA with edema (ARIA-E), which can be observed on MRI as brain edema or sulcal effusions, and ARIA with hemosiderin deposition (ARIA-H), which includes microhemorrhage and superficial siderosis. ARIA-E or ARIA-H may occur in isolation or concurrently. ARIA-H frequently occurs in association with an occurrence of ARIA-E. Similar to our conclusions from the original submission, the evidence presented by the applicant supports that lecanemab treatment is associated with an increased risk of ARIA. In this review, ARIA is defined as ARIA-E or ARIA-H microhemorrhage or superficial siderosis. Unlike the Applicant's presentation, macrohemorrhage including cerebral hemorrhage are not included under the term ARIA and will be described separately.

For definitions and management of ARIA, please refer to Appendix Section12.1.8.

Analysis of ARIA

Incidence of ARIA in 301 Core

Consistent with the findings in 201 Core as noted in currently approved lecanemab labeling and consistent with the findings from other monoclonal antibodies directed against aggregated forms of beta amyloid , lecanemab can cause ARIA, including ARIA-E and ARIA-H. Table 18**,** below, shows the incidence of ARIA events within 30 days of a dose of lecanemab in 301 Core.

Table 18 Incidence of Treatment Emergent ARIA or Cerebral Hemorrhage in Study 301 Core

Parameter	Placebo (N = 897) n (%)	Lecanemab (N = 898) n (%)
Total ARIA	84 (9%)	191 (21%)
ARIA-E	15 (2)	113 (13%)
Isolated ARIA-E	4 (0.4)	36 (4%)
Co-occurrence of ARIA-E and H[1]	8 (0.9)	74 (8%)
Not Co-occurring concurrent ARIA-E with ARIA-H[2]	3 (0.3)	3 (0.3)
ARIA-H[3]	80 (9)	152 (17)
Isolated ARIA-H	69 (8)	78 (9)
Cerebral Hemorrhage > 1 cm	0)	6 (0.7)

Source: Extracted from Clinical Analyst created table. [tariasum1.rtf] [tariasum1.sas] 12APR2023, 09:49,
[1]: ARIA-H happened before resolution of treatment emergent ARIA-E regardless of whether the ARIA-H was a treatment emergent event or not.

[2]: Subjects with treatment emergent ARIA-E and ARIA-H, and ARIA-H occurred either before an ARIA-E event occurred or occurred after the resolution of an ARIA-E event.
[3:] Subjects with treatment emergent ARIA-H. 2 subjects in Co-occurrence of ARIA-E and H did not have treatment Emergent ARIA-H
[4] Numbers based on PT of cerebral hemorrhage > 1 cm occurring 40 days after last dose of study drug.

The overall incidence of ARIA in 301 Core is higher than that observed in 201 Core where ARIA occurred in 12% on lecanemab and 5% on placebo. This is mainly driven by an increase in the incidence of ARIA-H in 301 Core that is higher than observed in 201 Core (6% on lecanemab vs 5% on placebo). The increased incidence of ARIA overall and the increased incidence of ARIA-H in 301 Core compared to 201 Core may possibly have been due to the larger number and longer follow up of ApoE ε4 carriers in 301 Core. Risk of cerebral hemorrhage was higher in those receiving lecanemab (0.7 % on lecanemab vs 0 on placebo).

The majority of ARIA-H events were microhemorrhages. Both microhemorrhages and superficial siderosis occurred at a higher incidence on lecanemab compared to placebo. (Table 19).

Table 19 Incidence of Treatment Emergent ARIA-H in 301 Core

Preferred Terms	Placebo (N = 897) n (%)	Lecanemab (N = 898) n (%)
ARIA-H	80 (9)	152 (17)
Amyloid related imaging abnormality-microhemorrhages and hemosiderin deposits	68 (8)	126 (14)
Superficial siderosis of central nervous system	21 (2)	50 (6)

Source: Clinical Analyst Created: Safety population and TRTEMFL = Y, [taearia1.rtf] [taearia1.sas] 21APR2023, 10:3.

As discussed in the original review, similar observation of co-occurrence of ARIA-E and ARIA-H, and presence of a higher incidence of ARIA-H in those with ARIA-E has been observed in studies of other monoclonal antibodies against amyloid. [18,19]**Error! Bookmark not defined.** These findings suggest that ARIA-E and ARIA-H are related phenomena, and likely are related to changes in vascular permeability, resulting from the processes leading to removal of amyloid during treatment with anti-amyloid antibodies. As described by Sperling et al, it is possible that depending on the location of the vessel, in the parenchyma versus meninges, leakage of proteinaceous fluid could

[18] Sperling R, Kack CR, Black SE, Forsch MP, Greenberg SM, Hyman BT, Scheltens P, Carrillo MC, Thies W, Bednar MM, Black RS, Brashear HR, Grundman M, Siemers ER, Feldman HH, Schindler RJ. Amyloid-related imaging abnormalities in patients with Alzheimer's disease treated with bapineuzumab: A retrospective analysis. Lancet Neurol. 2012 March; 11(3): 241–249
[19] Salloway S, Chalkias S, Barkhof F, Burkett P, Barakos J, Purcell D, Suhy J, Forrestal F, Tian Y, Umans K, Wang G, Singhal P, Haeberlein SB, Smirnakis K. Amyloid-Related Imaging Abnormalities in 2 Phase 3 Studies Evaluating Aducanumab in Patients with Early Alzheimer's Disease. Jama Neurology. JAMA Neurol. 2022;79(1):13-21. doi:10.1001/jamaneurol.2021.4161

give rise to an increased signal detected on FLAIR images (ARIA-E) in the brain parenchyma (vasogenic edema) and leptomeningeal spaces (sulcal effusions), while leakage of red cells would result in ARIA-H, seen on T2*GRE MRI as cerebral microhemorrhages and hemosiderosis.[18]

Incidence of ARIA in 301 OLE

In the 301 OLE alone, with a data cut off of December 1, 2022, the incidence of ARIA-E was 8% and ARIA-H was 13%. (Table 20). These rates are lower compared to the 301 Core incidence of ARIA-E and ARIA-H (13% and 17%) because this study population includes 671 subjects that have already been exposed to lecanemab for up to 18 months at the time of enrollment in the OLE. As most ARIA-E occurs during the first 3 months of exposure to study drug, the lower ARIA rate is not unexpected.

The incidences of treatment emergent ARIA, ARIA-E, and ARIA-H in the 714 subjects who were new exposures to lecanemab in 301 OLE (placebo in Core) were 20% (140/714), 14% (98/714), and 15% (110/714), respectively, similar to the incidence in 301 Core (Table 59). The incidence of treatment emergent cerebral hemorrhage in the new exposures in the 301 OLE was 0.4% (3 /714). Subject (b) (6) who had a nontreatment emergent cerebral hemorrhage 92 days after the last dose of lecanemab and subsequent to a brain biopsy during the OLE is not included in this number.

Table 20 Incidence of Treatment Emergent ARIA and Cerebral Hemorrhage in the 301 OLE Period Alone

Preferred Terms	**Lecanemab (N =1385)** n (%)
ARIA	209 (15)
ARIA-E	110 (8)
ARIA-H	176 (13)
ARIA-H microhemorrhage	159 (11)
Superficial siderosis	47 (3)
Cerebral hemorrhage*	3 (0.2)

Source: Clinical Analyst Created. Safety population and TRTEMFL = Y, [taearia4.rtf] [taearia4.sas] 27APR2023, 08:08
ARIA-E: Amyloid Related Imaging Abnormality edema/effusion
ARIA-H Amyloid related imaging abnormality hemosiderin depositions
** This table does not include a nontreatment emergent cerebral hemorrhage in subject (b) (6)*
** Includes cerebral hemorrhage occurring within 40 days of last dose (Subject (b) (6) with a cerebral hemorrhage 91 days after last dose of study drug not included)*

Incidence of ARIA-E and ARIA-H in 201 OLE

As of data cut off of December 01, 2022, there was one new ARIA-E, and 2 new ARIA-H microhemorrhages compared to the original review. The overall incidence of ARIA-E was remained 8%, and ARIA-H incidence went up from 14% to 16% (Section 12.1.9 Table 64).

Impact of ApoE ε4 Allele Status on Frequency of ARIA

ApoE ε4 homozygotes have been previously shown to have an increased incidence of symptomatic and overall ARIA compared to heterozygotes and noncarriers in subjects taking monoclonal antibodies directed against aggregated forms of beta amyloid, including lecanemab, as described in the currently approved lecanemab label.

Study 301 Core

While in 201 Core only 30% of the subjects at the proposed dose arm were ApoE ε4 allele carriers due to protocol amendments, 69% of subjects in the lecanemab arm in 301 Core were carriers of the ApoE ε4 allele (Table 5). The findings from 301 Core show an increased risk of ARIA-E and ARIA-H in ApoE ε4 carriers with the highest incidence observed in ApoE ε4 homozygotes. (Table 21)

Table 21 Incidence of Treatment Emergent ARIA and Cerebral Hemorrhage > 1cm by ApoE Genotype in 301 Core

	Homozygote		Heterozygote		Noncarriers	
	PBO (N=133) n (%)	Lecanemab (N=141) n (%)	PBO (N=478) n (%)	Lecanemab (N=479) n (%)	PBO (N=286) n (%)	Lecanemab (N=278) n (%)
ARIA	29 (22)	63 (45)	44 (9)	91 (19)	11(4)	37 (13)
ARIA-E	5 (4)	46 (33)	9 (2)	52 (11)	1 (0.3)	15 (5)
ARIA-H	28 (21)	54 (38)	41 (9)	66 (14)	11 (4)	32 (12)
ARIA-H microhemorrhage	25 (19)	48 (34)	34 (7)	58 (12)	9 (3)	20 (7)
Superficial Siderosis	6 (5)	18 (13)	13 (3)	19 (4)	2 (1)	13 (5)
Cerebral Hemorrhage* > 1 cm	0 (0)	2 (1)	0 (0)	3* (0.6)	0 (0)	1 (0.4)

Source: Clinical Analyst Created. Safety population and TRTEMFL = Y;[taeariaapoe1.rtf] [taeariaapoe1.sas] 12APR2023, 12:2
** Includes cerebral hemorrhage within 40 days after last dose of study drug (subject (b) (6) with cerebral hemorrhage 40 days after last dose on lecanemab included, and excludes (b) (6) with cerebral hemorrhage > 90 days after last dose on placebo).*

ApoE ε4 and ε2 alleles have been associated with increased risk of intracerebral hemorrhage.[20] In 301 Core the incidence of cerebral hemorrhage was 0/611 in ε4 carriers on placebo versus 5/620 in ε4 carriers on lecanemab. Interpretation of these data with respect to the risk of cerebral hemorrhage in ApoE ε4 carriers on lecanemab is limited because out of the 5 ε4

[20] *Marini S, Crawford K, Morotti A, Lee M, Pezzini A, Moomaw C, Flaherty M, Montaner J, Roquer J, Jimenez-Conde J and other members of the International Stroke Genetics Consortium. Association of Apolipoprotein E With Intracerebral Hemorrhage Risk by Race/Ethnicity. JAMA Neurol. 2019;76(4):480-491. doi:10.1001/jamaneurol.2018.4519*

carriers with cerebral hemorrhage, 2 homozygotes were on anticoagulation, and one heterozygote patient was on an antithrombotic prior to cerebral hemorrhage.

The risk of SAEs and of symptomatic ARIA was also greater in ApoE ε4 homozygotes than in ApoE ε4 heterozygotes and noncarriers (Table 22)

Table 22 Summary of ARIA by ApoE Genotype on Lecanemab in 301 Core

	Lecanemab N=898 N (%)		
Adverse Event	Noncarriers N=278 n (%)	Heterozygote N=479 n (%)	Homozygote N=141 n (%)
ARIA-E	15(5)	52(11)	46(33)
SAES	2(0.7)	2(0.4)	3(2)
Discontinuations	3(1)	2(0.4)	9(6)
Interruptions	7(2)	29 (6)	34 (24)
Symptomatic	4(1.4)	8(2)	13(9)
ARIA-H	32(12)	66(14)	54(38)
SAES	1(0.4)	0	1(0.7)
Discontinuations	2(0.7)	5(1)	10(7)
Interruptions	3 (1)	18 (4)	20 (14)
Symptomatic	2(0.7)	4(1)	5(4)

Extracted from clinical analyst created tables using adae.xpt.

301 OLE

Findings from the OLE period are similar to the observation in 301 Core, namely that ApoE ε4 homozygotes have the highest risk of ARIA-E and ARIA-H (Table 23). The numbers of events were driven by new exposures in 301 OLE (Table 59). The risk associated with ApoE ε4 was also observed in 201 OLE (Section 12.1.9)

Table 23 Incidence of Treatment Emergent ARIA by ApoE Genotype in 301 OLE

	Noncarriers N=423 n (%)	Heterozygotes N=760 n (%)	Homozygotes N=202 n (%)
ARIA	37 (9)	105 (14)	67 (33)
ARIA-E	17 (4)	51 (7)	42 (21)
ARIA-H	31 (7)	89 (12)	56 (28)
ARIA-H microhemorrhage	24 (6)	82(11)	53 (26)
Superficial Siderosis	9 (2)	24 (3)	14 (7)

	Noncarriers N=423 n (%)	Heterozygotes N=760 n (%)	Homozygotes N=202 n (%)
Cerebral Hemorrhage > 1 cm *	1 (0.2)	1 (0.1)	1(0.5)

Source: Clinical Analyst Created: Safety population and TRTEMFL = Y, [taeariaapoe4.rtf] [taeariaapoe4.sas] 27APR2023, 08:08
**Subject (b) (6) who had a nontreatment emergent cerebral hemorrhage 91 days after last dose of study drug not included*

Reviewer Comment: Risk of both ARIA-E and ARIA-H was highest in ApoE ε4 homozygotes compared to heterozygotes or noncarriers in lecanemab treated subjects. As noted below, the incidence of symptomatic ARIA was also increased in ApoE ε4 carriers. *This suggests that the discussions around risk of ARIA with lecanemab treatment with patients would benefit from knowledge of ApoE genotype to better inform the potential risks.*

Radiographic Severity of ARIA

See Table 53 and Table 54 for the definitions used to rate the severity of ARIA-E and ARIA-H based on radiographic findings.

Among the 898 subjects treated with lecanemab in 301 Core, maximum radiographic severity of ARIA-E and ARIA-H was as follows: 4% had radiographically mild ARIA-E, 7% radiographically moderate ARIA-E , and 1% radiographically severe ARIA-E; 9% percent had radiographically mild ARIA-H microhemorrhage, 2% moderate and 3% radiographically severe, and 4 % had radiographically mild, 1% radiographically moderate and 0.4% radiographically severe superficial siderosis (Table 67). The findings in 301 OLE (Table 68) and in 201 OLE are consistent with those in 301 Core alone. The findings are generally consistent with those observed in 201 Core; differences are likely due to increased exposure with a larger clinical trial database in 301 Core.

A full accounting of ARIA radiographic severity in 301 Core, 301 OLE, 301 Core and OLE combined, and 201 OLE is shown in Table 65, Table 66, Table 67, Table 68 in the Appendix Section 12.1.9.

Across genotypes, most ARIA-E was mild or moderate. Radiographic severity of ARIA in patients on lecanemab, by Apo E genotype was as follows:

Table 24 ARIA Radiographic Severity by ApoE Genotype on Lecanemab in 301 Core

	APO E ε4 noncarriers	**APO E ε4 heterozygotes**	**APO E ε4 homozygotes**
ARIA E	n=15	n=51	n=46
Mild	6/15 (40%)	25/51 (49%)	6/46 (13%)
Moderate	9/15 (60%)	24/51 (47%)	33/46 (72%)
Severe	0	2/51 (4%)	7/46 (15%)
ARIA H	n=32	n=66	n=54
Mild	27/32 (84%)	48/66(73%)	22/54 (41%)
Moderate	2/32 (6%)	9/66 (14%)	13/54 (24%)
Severe	3/32 (9%)	9/66 (14%)	19/54 (35%)

Extracted from Clinical Analyst created table:
Safety population and TRTEMFL = Y,[taeariasevapoeexmac1.rtf] [taeariasevapoeexmac1.sas] 15JUN2023, 13:15
** ARIA-E radiographic severity was missing in one ApoE ε4 heterozygote patient*

Incidence of SAEs, discontinuations and TEAEs attributed to ARIA

The incidences of SAEs, discontinuations, and TEAEs attributed to ARIA in 301 Core were higher in the lecanemab arm compared to placebo. Please refer to Table 10 (SAEs), Table 12 (Discontinuations), and Table 18 (TEAEs), and to ARIA summary Tables, Table 69, Table 70, Table 71, Table 72 for 301 Core, 301 OLE, 301 Core and OLE and 201 OLE in Appendix Section 12.1.9 .

There was one death ((b) (6) due to complications of ARIA-E in 301 OLE in a patient who had severe ARIA-E, resulting in a seizure, aspiration pneumonia and death due to acute respiratory failure. This subject is described under Section 7.4.1 Deaths.

Clinical Symptoms Associated with ARIA

301 Core

The majority of ARIA cases in 301 Core were asymptomatic, similar to the findings in 201 Core in the original BLA. In Study 301 Core, symptomatic ARIA occurred in 29 out of 898 (3.2%) of subjects treated with lecanemab compared to 2 out of 897 (0.2%) on placebo. In 301 Core, 2.8% of patients treated with lecanemab had symptomatic ARIA-E and 1% had symptomatic ARIA-H**. (**Table 25). SAEs of ARIA-E occurred in 0.8% (7/898) patients on lecanemab vs none on placebo. SAEs of ARIA-H occurred in 0.3% (2/898) on lecanemab vs none on placebo.

The most common symptom observed in patients with ARIA-E was headache (12/898, 1.3% overall; 12/25, 48% of patients with ARIA-E); other reported symptoms included confusional state, dizziness, nausea, combination of different visual changes, other focal neurologic deficits, and seizure. Symptoms for ARIA-H were similar to ARIA-E with the most common observed symptoms including confusional state, dizziness, and headache. A complete list of symptoms is found in Table 81.

Table 25 Incidence of Treatment Emergent Symptomatic ARIA in 301 Core

	Placebo N=897 N (%)	Lecanemab N=898 N (%)
ARIA overall	2 (0.2)	29 (3)
ARIA-E	0	25 (3)
ARIA-H	2(0.2)	11 (1)
ARIA-H-microhemorrhage	2 (0.2)	9 (1)*
Superficial Siderosis	0	2 (0.2)
Cerebral Hemorrhage**	0	3(0.3))

Source: Clinical Analyst Created. Safety population and TRTEMFL = Y, [taeariasysexmac1.rtf] [taeariasysexmac1.sas] 28APR2023, 10:44
**Two subjects with nontreatment emergent symptomatic ARIA-H microhemorrhage events were not counted in the above table: Subject (b) (6) had treatment emergent ARIA-E followed by nontreatment emergent ARIA-H both associated with partial seizure with secondary generalization, and subject (b) (6) who had nontreatment emergent ARIA-H microhemorrhage and associated headaches*
*** Includes cerebral hemorrhage occurring within 40 days after last dose of study drug (b) (6))*

Of the 29 patients on lecanemab with symptomatic ARIA, 13/29 (44.9%) were ApoE ε4 homozygotes, 12/29 (41.4%) were heterozygotes and 4/29 (13.8%) were noncarriers.

Of the 25 symptomatic ARIA-E events, the worst clinical symptom severity was mild in 12, moderate in 11, and severe in 2 subjects on lecanemab. Of the 2 subjects with symptomatic superficial siderosis both had a clinical severity characterized as mild.

Six out of 29 symptomatic ARIA events were deemed to be serious events, occurring in 2 ApoE ε4 homozygotes, 2 ApoE ε4 heterozygotes and 2 ApoE ε4 noncarriers. These were all serious ARIA-E events, with one subject also having a co-occurring serious symptomatic ARIA-H (Table 79) .

The radiographic severity did not consistently correlate with the clinical severity.

In 301 Core, in the 25 subjects who had symptomatic ARIA-E on lecanemab, study drug was withdrawn in 11, interrupted in 12, and dose not changed in 2 as a result of the symptomatic ARIA-E. Six subjects received concomitant medications for symptomatic ARIA-E, four of which were serious events. Two subjects with symptomatic ARIA-E (b) (6)) initially complained of a headache (rated as mild or moderate in clinical severity) and were dosed through the headache only to find out on subsequent MRI that they had severe ARIA-E. Both of these subjects were ApoE ε4 homozygotes. See Section 14.1.2 for selected narratives. In the 9 subjects who had symptomatic ARIA-H microhemorrhage, study drug was withdrawn in 3, interrupted in 5, and dose was not changed in 1. Of the 2 with symptomatic superficial siderosis, study drug was withdrawn in one, and interrupted in another.

Reviewer Comment: In addition to the cases described above, both of the subjects who died due to lecanemab related AEs, cerebral hemorrhage ([(b) (6)] and ARIA-E and seizure ([(b) (6)] complained of headaches which were dosed through and not attributed to study drug. Both also were ApoE ε4 homozygotes. Clinicians should have a low threshold to obtain imaging, even in the setting of mild headaches, in ApoE ε4 carriers who are at higher risk of having severe ARIA-E. Currently approved labeling recommends that if a patient experiences symptoms suggestive of ARIA, clinical evaluation should be performed, including MRI if indicated.

Clinical symptoms associated with ARIA recovered/resolved without sequela in 22/29 (76%), recovered/resolved with sequela in 1/29 subject, were recovering/resolving in 2/29 subjects, and were not recovered in 4/29 subjects within the period of observation.

Clinical symptoms of ARIA-E resolved completely in 23/25 (92%) symptomatic subjects, resolved with sequela in one subject, and did not resolve in one subject within the period of observation. One subject with symptomatic ARIA-E was continuing to have headaches (which was a symptom of the ARIA-E) at the time of discontinuation from the study and another patient who had a partial seizure with secondary generalization, was considered to be resolved with sequela as he remained on an antiepileptic drug at the time of discontinuation from the study. Symptomatic ARIA-H resolved completely in 6/11 subjects (54%), was recovering/resolving in 2/11 subjects, and was not recovered/resolved in 3/11 subjects within the period of observation. For details, please refer to Table 73 in the Appendix.

301 OLE

The incidence of symptomatic ARIA of 2.5% (34/1385), symptomatic ARIA E of 2.1% (29/1385), and serious symptomatic ARIA of 0.6% (8/1385) in 301 OLE, were similar to the incidence of symptomatic ARIA observed in 301 Core. A list of symptoms is shown in Table 82. In 301 OLE, almost all the symptomatic ARIA-E occurred in patients newly exposed to lecanemab. Two subjects who received lecanemab in 301 Core and did not experience ARIA during this time, had symptomatic ARIA during their participation in 301 OLE. Subject [(b) (6)], an ApoE ε4 noncarrier who did not have any ARIA-E during the 301 Core, had 2 ARIA-E events in 301 OLE; the second event was symptomatic with confusion and occurred after the 52nd dose of lecanemab (20th dose in OLE). Subject [(b) (6)], an ApoE ε4 homozygote, had serious symptomatic, radiographically severe ARIA-E with seizures after the 41st dose of lecanemab (3rd dose in OLE) in the setting of 53 new microhemorrhages.

Reviewer Comment: The two cases of ARIA-E in subjects who have received 18 months of study drug is unusual, given that ARIA -E usually occurs during the first 3 months of treatment.

Sixteen subjects (16/1385, 1%), 14 of whom were new exposures in 301 OLE, had symptomatic ARIA-H during the 301 OLE. Three out of 16 symptomatic ARIA-H events were serious.

Please see Section 12.1.9 narratives of the Serious and Symptomatic ARIA cases. Please also see Table 79 for summary of all the Serious Symptomatic ARIA cases in 301 Core and OLE.

201 OLE

In Study 201 OLE, 3 of the 15 subjects with ARIA-E had clinical symptoms including headache in one subject and both headache and dizziness in two subjects. All three ARIA-E events had concurrent ARIA-H. None of the ARIA-H events in 201 OLE was identified as symptomatic in the dataset. There was one symptomatic cerebral hemorrhage in the 201 OLE study (See Section 7.5.2).

Timing of ARIA

301 Core

In Study 301 Core the majority of ARIA-E in those receiving LEC10-BW was observed within the first 3 months (Figure 1, obtained from Study 301 Core CSR).

Figure 1 Kaplan-Meier Plot of Time to First ARIA-E Event – Study 301 Core (Safety Analysis Set) (obtained from applicant document summary of clinical safety)

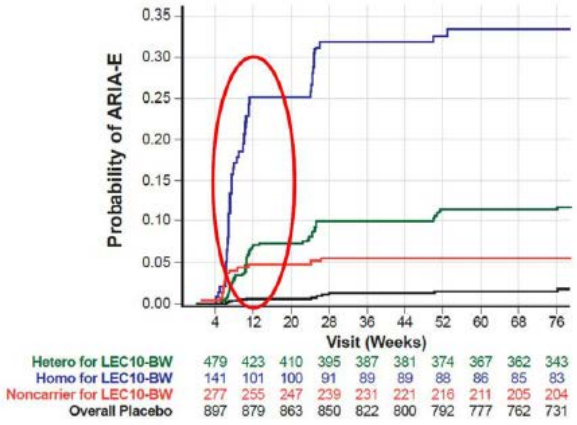

Figure 3 Kaplan-Meier Curve of Time to First ARIA-E – Study 301 Core (Safety Analysis Set)

ARIA = amyloid-related imaging abnormality-edema/effusion, hetero = heterozygous, homo = homozygous.
Source: Study 301 Core CSR Figure 14.3.2.6.1, Table 14.3.2.6.17, and Table 14.3.2.6.18.

In 301 Core in those on lecanemab, 47% (53/113) of ARIA-E events occurred before the 5th dose, 72% (81/113) prior to the 7th dose, and 92% (104/113) occurred prior to the 14th dose. (Table 26). Findings were similar in 301 Core and OLE combined, and in 201 OLE Table 72, Table 73), and among ApoE ε4 homozygotes alone in 301 Core (Table 27).

In 301 Core, the first treatment emergent ARIA-E on lecanemab on average lasted for 92 days (SD 58, range 16-374) before it resolved in subjects receiving LEC10BW.

Table 26 Timing of first ARIA-E Events on Lecanemab in Study 301 Core

Numbers of Dose Prior ARIA-E	Number of subjects experiencing a first ARIA-E event (n=113)	Cumulative frequency of first ARIA-E N (%)
1	1	1 (1)
2	1	2 (2)
3	7	9 (8)
4	44	53 (47)
5	4	57 (50)
6	24	81 (72)
11	2	83 (73)
12	6	89 (79)
13	15	104 (92)
21	1	105 (93)
22	1	106 (94)
23	1	107 (95)
24	3	110 (97)
25	1	111 (98)
26	1	112 (99)
39	1	113 (100)

Table 27 Timing of First ARIA-E Events in ApoE ε4 Homozygotes on Lecanemab in Study 301 Core

Numbers of Dose Prior ARIA-E	Number of subjects experiencing a first ARIA-E event (n=46)	Cumulative frequency of first ARIA-E N (%)
2	1	1 (2)
3	4	5 (11)
4	21	26 (56)
6	9	35 (76)
12	2	37 (80)
13	7	44 (96)
21	1	45 (98)
23	1	46 (100)

Subjects with Multiple ARIA Events

In 301 Core 75.2% (85 out of 113) of lecanemab-treated patients with ARIA-E had a single treatment emergent ARIA-E event. The incidence of having more than one treatment emergent ARIA-E event was 25% (28 out of 113) on lecanemab vs 7% (1 out of 15) on placebo (b) (6)). Of the lecanemab-treated subjects who had multiple ARIA-E events 4 subjects had more than two ARIA-E events.

Overall, across the development program, the experience with multiple episodes of ARIA is too limited to make generalizations about risk factors for multiple events, serious or severity of events or outcomes. Similarly, the clinical studies only allowed for continued dosing in the setting of asymptomatic, radiographically mild ARIA-E or for asymptomatic mild or moderate ARIA-H, and otherwise required dosing interruption. Thus, there is no experience in Study 301 Core or OLE or in 201 OLE with continued dosing for symptomatic, radiographic mild ARIA-E that is allowed for in the approved label. See Section 12.1.9 for selected narratives of subjects with multiple ARIA events.

Late occurring ARIA

Late occurring ARIA, defined in this review as incident ARIA events occurring beyond 30 days after a dose of study drug were observed in 301 Core. These ARIA events occurred either while the study drug was interrupted (without further doses received since the last dose) or the dose was the last dose in the study. While there were no subjects who had late-occurring ARIA-E events, there were a higher number of subjects who had late occurring ARIA-H events in the lecanemab arm compared to placebo (Table 28).

Table 28 Incidence of ARIA-H Occurring 30 Days After a Dose in 301 Core

Preferred Terms	Placebo (N = 897)	Lecanemab (N = 898)
ARIA-H	5 (0.6%)	44 (4.9%)
Amyloid related imaging abnormality-microhemorrhages and hemosiderin deposits	4 (0.4%)	40 (4.5%)
Superficial siderosis of central nervous system	1 (0.1%)	13 (1.4%)

Safety population and TRTEMFL = Y
[tcheckaeariagt30days1.rtf] [tcheckaeariagt30days1.sas] 25MAY2023, 07:51

Almost all subjects who had a late occurring ARIA-H event were ApoE ε4 carriers except 2 subjects in the lecanemab group: 28/44 on lecanemab and 3/5 on placebo were ApoE ε4 homozygotes, 14/44 on lecanemab and 2/5 on placebo were ApoE ε4 heterozygotes, and 2/44 and none on the placebo arm were noncarriers. Longest time since last dose to late occurring ARIA-H events (3 subjects had 2 late occurring ARIA-H events) was on average 96 days (range 32-359 days) on lecanemab, and 75 days (34 to 129 days) for placebo.

Of the late occurring ARIA-H microhemorrhage events, 21 in the lecanemab arm were radiographically severe (meaning cumulative accumulation of over 10 microhemorrhages), while none was severe on placebo.

I will provide selected representative narratives for a few subjects on lecanemab who had a late occurring ARIA-H.

Subject (b) (6) is a 74-year-old ApoE ε4 homozygote who on screening MRI had 2 microhemorrhages in the left temporal area. He was not on an antithrombotic. After the 4th, 5th, 12th and 17th doses of study drug this subject experienced 4 episodes of treatment emergent ARIA-H events. After the 4th dose of study drug, he sustained 3 new microhemorrhages and a single event of superficial siderosis. After the 5th dose of study drug, he sustained 1 new microhemorrhage and superficial siderosis. After the 12th dose of study drug on study day 170 he sustained 16 new microhemorrhages, for a cumulative total of 22 microhemorrhages (inclusive of 2 microhemorrhages at baseline). At this time, he also had a new superficial siderosis along with mild ARIA-E. Study drug was temporarily interrupted for these events and restarted on study day 226. He received the 17th dose of study drug on study day 308. On study day 309 he had 2 new microhemorrhages cumulatively adding up to 24. Study drug was permanently withdrawn. On study day 341 (33 days after the last dose of study drug) he sustained 15 new microhemorrhages for a total of 39 microhemorrhages. On study day 392, 84 days after the last dose of study drug, he had 2 new microhemorrhages for a total of 41 microhemorrhages. He was symptomatic with mild headaches. He also experienced three new areas of superficial siderosis. This subject was discontinued from study due to four episodes of ARIA-H.

Reviewer Comment: In this case the subject had 2 microhemorrhages at baseline. He started sustaining more microhemorrhages during the course of treatment with lecanemab but continued to have them over 80 days after discontinuation of study drug. Whether these late occurring microhemorrhages are due to underlying cerebral amyloid angiopathy, lecanemab or the combination of both is difficult to ascertain.

Subject (b) (6) is described under Section 7.4 Discontinuations. This is a 68-year-old female who was ApoE ε4 homozygous, who had 1 microhemorrhage at the screening MRI and was on a baby aspirin daily. She received the 3rd dose of study drug on study day 28. On study day 44, there was report of worsening confusion, and poor vision. On study day 45, she received the 4th dose of study drug (last dose). On study day 50, 17 days after the last dose of study drug prior to ARIA (presuming that symptom onset prior to the second dose was related to ARIA-E), MRI identified radiographically moderate ARIA-E and 174 new microhemorrhages for a total of 175 microhemorrhages. Study drug was permanently discontinued. On study day 161, ARIA-H remained stable. On study day 190, 146 days after the last dose of study drug the subject had new 2 new ARIA-H microhemorrhages for a cumulative of 177. The subject withdrew consent and discontinued study.

Reviewer Comment: In this case, similar to the subject discussed above, I cannot rule out underlying amyloid angiopathy, given her baseline MRI showing a single, pretreatment microhemorrhage, the very high number of microhemorrhages that were sustained during lecanemab treatment, and finally microhemorrhages occurring ~5 months after the last dose of study drug. This subject sustained an unusually high number of treatment emergent ARIA-H. Whether this is the result of lecanemab treatment alone, or lecanemab treatment superimposed

on underlying cerebral amyloid angiopathy is not known. Additionally, the cognitive consequences of having sustained this number of ARIA-H is also not established, since in population studies presence of microhemorrhages on MRI or postmortem, is usually associated with poorer cognitive function during life.

Reviewer Comment: While late occurring ARIA-H events have been observed in ApoE ε4 carrier subjects on placebo in 301 Core, they appear to occur at higher frequency in those that have received lecanemab. While these may be a result of the evolution of vascular permeability during the removal of amyloid from the vasculature in patients treated with lecanemab, spontaneous ARIA-H has been observed in the absence of lecanemab especially in ApoE ε4 carriers. The reason for this observation and the relationship between late occurring ARIA-H and lecanemab is unknown.

Late occurring ARIA-E and ARIA-H was also observed in study 301 OLE

During the 301 OLE 1.2% (17 out of 1391) subjects had a late occurring ARIA-H event. There were 16 subjects with ARIA-H microhemorrhages, and 6 with superficial siderosis, 5 had both ARIA-H and superficial siderosis. Of these 17 subjects 41.2% (7) were ApoE e4 homozygote, 62.9% (9) were heterozygote, and 5.9% (1) was a noncarrier. Seven out of 17 subjects had more than one late occurring ARIA-H event, and all subjects only had one late occurring superficial siderosis event. These late occurring ARIA-H events occurred on average 55.5 days after the last dose of study drug (SD 24.2, range 31 to 114). Five of the ARIA-H events were associated with a concurrent symptomatic ARIA-E. Two of the ARIA-H events were symptomatic ((b) (6)). See Appendix 12. 1.9 for the narrative for subject (b) (6)

Radiographic Duration of ARIA

In Study 301 Core, the mean duration of ARIA-E in the LEC10 BW arm was 92 days (~ 13 weeks), ranging between 16-374 days (~2-55 weeks) (Table 76).

The first ARIA-E event in those on lecanemab resolved by the 12th week in 52% (59 out of 113), by 17 weeks in 81% (91 out of 113), and in all subjects eventually during the course of the study. In 19% (22 out of 113) of subjects resolution of ARIA-E took longer than 17 weeks and in 10% ARIA-E took longer than 21 weeks to resolve. The duration of ARIA-H cannot be reliably calculated because in most cases ARIA-H does not resolve on MRI.

Of the 110 first ARIA-E events occurring during the OLE period, in 23 the ARIA-E was ongoing as of data cut off of December 1, 2022. Of the 87 subjects in whom the first ARIA-E episode resolved the mean duration of the first ARIA-E event was 84 days (~12 weeks), ranging between 22-308 days (~3 -44 weeks). In 301 OLE, time to resolution was similar to that observed in 301 Core. Of those 87 subjects the first ARIA-E resolved in 48% (42 out of 87) by 12 weeks, in 81%

(70 out of 87) by 17 weeks, and in 91% (79 out of 87) by 21 weeks. In the remaining 8/87 subjects ARIA-E resolved over 21 weeks.

Effect of Antithrombotic Medications on ARIA risk

In Study 301, unlike Study 201, anticoagulation was allowed. Subjects who were on anticoagulants at screening were required to have their anticoagulation status optimized and stable for at least 4 weeks before Screening. Subjects who were on anticoagulant therapy were not permitted to participate in CSF assessments (revised per Amendment 05). Subjects who required treatment with thrombolytic drugs did not have to be discontinued from the study, but study drug was temporarily suspended for these subjects during thrombolytic therapy until stabilization or resolution of the medical condition that required thrombolytic drug treatment. The protocol also excluded subjects with an increased risk for hemorrhage: subjects with a bleeding disorder that was not under adequate control (including a platelet count < 50,000 or international normalized ratio [INR] > 1.5 for subjects who are not on anticoagulant treatment, e.g., warfarin; revised per Amendments 04 and 05). Additionally, any subjects with more than 4 microhemorrhages (defined as 10 mm or less at the greatest diameter), a single macrohemorrhage greater than 10 mm at greatest diameter, an area of superficial siderosis, aneurysms, or vascular malformations were excluded.

The majority of exposures to antithrombotic medications in 301 Core were to aspirin (76%, 490/646). The use of antithrombotics did not appear to increase the risk of ARIA-H (microhemorrhage or superficial siderosis) while on lecanemab in 301 Core, consistent with the findings in 201 Core described in the approved label. There did appear to be a small but higher risk of cerebral hemorrhage in those receiving lecanemab versus placebo, which increased with antithrombotic use. (Table 29). This was most pronounced in those on anticoagulation. Similar findings were observed in combined Core and OLE.

Table 29 Incidence of ARIA and Cerebral Hemorrhage with Anti-Thrombotic Use Preceding ARIA -H or Cerebral Hemorrhage in 301 Core[a]

	ARIA-H		Cerebral Hemorrhage*	
	Lecanemab	Placebo	Lecanemab	Placebo
Not on antithrombotic	93 / 545 (17)	49 / 584 (8.4)	3 / 545 (0.6)	0/584
On antithrombotic	55 / 328 (17)	29 / 304 (10)	3[b] / 328 (0.9)	0/304
Aspirin ≤ 81 mg alone	29 / 162 (18)	13 / 144 (9)	0 / 162	0/144
Aspirin > 81 mg, other antiplatelet or combination of aspirin and another antiplatelet	15 / 116 (13)	9 / 107 (8)	1 / 116 (0.9)	0/107
Anticoagulation (alone or combined with other antithrombotic)	11 / 79 (14)	7 / 72 (10)	2 / 79 (2.5)	0/72

[a] Represents events of ARIA-H or cerebral hemorrhage that occurred between the time when the incident ARIA-H or cerebral hemorrhage was observed and the previous MRI when it was not observed; the denominator is the total number of individuals on a selected antithrombotic category during that window.
ARIA-H includes microhemorrhages and superficial siderosis
Source: May 1, 2023, Sponsor response to information request (Table sBLA IR9-1mod)
Modified to include cerebral hemorrhage occurring with 40 days after last dose of study drug. (excludes subject (b) (6) on placebo in whom cerebral hemorrhage occurred > 90 days after last dose of lecanemab).
[b] These were the antiplatelet drug ticagrelor and anticoagulants warfarin (combined with aspirin) and rivaroxaban.

Similar findings were observed in the combined 301 Core and OLE dataset (See Table 78).

Reviewer Comment: Based on the available data, albeit relatively small numbers, anticoagulation when added to lecanemab appears to increase the risk of cerebral hemorrhage.

MRI Monitoring and Approach to the Management of ARIA

In 301 Core, MRI imaging for ARIA was performed during screening, prior to the 5th, 7th, 14th, 27th, doses and 90 days post last dose. For subjects continuing into the OLE, the MRI performed prior to the 40th dose (Visit 42) was considered as the OLE baseline with the next safety MRI performed prior to the 5th dose in the OLE.

Similar to the original recommendations, I recommend continuing to perform safety MRIs for detection of ARIA-E during treatment with lecanemab prior to the 5th infusion, 7th infusion, and 14th infusion, which is consistent with current labeling based on the original submission as well as the timing of MRIs performed during the first 6 months in Study 301 CORE. This approach is supported by findings from the original review as well as the larger data from Study 301 Core. The Alzheimer's Disease and Related Disorders Therapeutics Work Group[21] recently developed a document with recommendations for use of lecanemab recommending an additional MRI prior to the 26th infusion in addition to the MRIs outlined in the current label, particularly in those who are ApoE ε4 carriers, and those that had ARIA on earlier MRIs. During Study 301 Core, 9 out of 113 ARIA-E events occurred between the 14th and 26th dose. All of these occurred after the 21st dose, with one event each occurring after the 21st, 22nd, 23rd , 25th and 26th doses and 3 events occurring after the 24th dose. Two out of 9 were ApoE ε4 homozygotes, and 6 were heterozygotes. None was symptomatic, and radiographic severity was moderate in 3, and mild in 5. Based on these findings from limited number of subjects, while it is not unreasonable to obtain an additional MRI somewhere between the 24th dose and 26th dose, the majority 91% of ARIA is likely to be captured with the currently labeled MRI monitoring timeline and the impact of a monitoring MRI prior to the 26th dose is not entirely clear.

[21] Cummings J, Apostolova L, Rabinovici GD, Atri A, Aisen P, Greenberg S, Hendrix S, Selkoe D, Weiner M, Petersen RC, Salloway S, for the Alzheimer's Disease and Related Disorders Therapeutics Work Group. Lecanemab: Appropriate Use Recommendations.
J Prev Alz Dis 2023; Published online March 27, 2023, http://dx.doi.org/10.14283/jpad.2023.30

Dosing recommendations for patients with ARIA-E or with ARIA-H, as provided for in currently approved labeling, are shown below. These continue to remain appropriate

Clinical Symptom Severity[1]	**ARIA-E Severity on MRI**		
	Mild	**Moderate**	**Severe**
Asymptomatic	May continue dosing	Suspend dosing[2]	Suspend dosing[2]
Mild	May continue dosing based on clinical judgment	Suspend dosing[2]	
Moderate or Severe	Suspend dosing[2]		

[1] Mild: discomfort noticed, but no disruption of normal daily activity. Moderate: discomfort sufficient to reduce or affect normal daily activity. Severe: incapacitating, with inability to work or to perform normal daily activity.

[2] Suspend until MRI demonstrates radiographic resolution and symptoms, if present, resolve; consider a follow-up MRI to assess for resolution 2 to 4 months after initial identification. Resumption of dosing should be guided by clinical judgment.

Clinical Symptom Severity	**ARIA-H Severity on MRI**		
	Mild	**Moderate**	**Severe**
Asymptomatic	May continue dosing	Suspend dosing[1]	Suspend dosing[2]
Symptomatic	Suspend dosing[1]	Suspend dosing[1]	

[1] Suspend until MRI demonstrates radiographic stabilization and symptoms, if present, resolve; resumption of dosing should be guided by clinical judgment; consider a follow-up MRI to assess for stabilization 2 to 4 months after initial identification.

[2] Suspend until MRI demonstrates radiographic stabilization and symptoms, if present, resolve; use clinical judgment in considering whether to continue treatment or permanently discontinue LEQEMBI.

In general, I agree with these dosing recommendations. I note that there continues to be insufficient data on the safety of continued dosing through radiographically mild ARIA-E with mild clinical symptoms. The Agency's rationale for the recommendation for dosing in this situation is that some symptoms, such as nausea or dizziness, may be vague and there may be uncertainty regarding the relationship of these symptoms to ARIA. In the aducanumab trial there were a few instances where patients were treated with aducanumab through mild symptomatic ARIA-E without adverse outcomes. Therefore, it was determined that prescribers should use clinical judgment in determining if the presence of mild symptoms were of clinical concern and should preclude dosing with aducanumab. During the 301 Core study, similar to the 201 OLE, dosing was discontinued for any symptomatic ARIA-E regardless of the radiographic severity of ARIA-E (in 201 Core any occurrence of ARIA-E led to discontinuation of

study drug). Despite this, in 3 subjects ([(b) (6)] dosing was not interrupted despite symptomatic ARIA-E. Subject [(b) (6)], an ApoE ε4 heterozygote, had a radiographically mild ARIA-E which was symptomatic with a moderate headache after the 12th dose of study drug. No action was taken with study drug in response to the ARIA-E, and he went on to receive 5 more doses of study drug, after which he withdrew from study. Subject [(b) (6)], an ApoE ε4 homozygote, also had a symptomatic radiographically mild ARIA-E event with symptoms of mild agitation after the 44th dose of study drug, and no action was taken with study drug and the subject received 2 more doses of study drug. No further ARIA related events were identified during the remainder of the study for [(b) (6)], and subject [(b) (6)] had one more ARIA-E event 64 days after the last dose of study drug which was asymptomatic. Subject [(b) (6)] had mild radiographic ARIA-E with symptom of headaches rated as moderate, however no action was taken with study drug and patient continued to be dosed without any further ARIA events. Subjects, [(b) (6)] and [(b) (6)] both complained of a mild headache shortly after starting lecanemab in the OLE. Both had fatal outcomes due to multiple cerebral hemorrhages ([(b) (6)] and severe ARIA-E complications ([(b) (6)] Whether they had ARIA-E and the severity if present, at the time of the initial complaint of mild headache is not known as these subjects did not receive unscheduled MRIs at the time they complained of headaches. Overall, there remains insufficient data on the safety of dosing through symptomatic mild ARIA-E. Because there is no new additional information in this dataset to add to the existing limited available safety data for this class of drugs on continued dosing in mild symptomatic and radiographically mild ARIA-E, continuing to rely on the clinical judgement of the treating physician, whether to continue dosing remains reasonable.

In patients who develop cerebral hemorrhage greater than 1 cm in diameter during treatment with lecanemab, current labeling recommends that dosing with lecanemab be suspended until an MRI demonstrates radiographic stabilization and symptoms, if present, resolve, and that prescribers should use clinical judgement in considering whether to continue treatment after radiographic stabilization and resolution of symptoms or permanently discontinue lecanemab. The rationale for this recommendation is that cerebral hemorrhages can occur in an older population and may have an etiology that is unrelated to cerebral amyloid angiopathy or treatment with an anti-amyloid monoclonal antibody, such as a hypertensive hemorrhage or trauma. Clinicians should consider the potential etiology of the hemorrhage and also the individual risk factors for a patient when deciding whether to continue or permanently discontinue treatment. This recommendation remains appropriate.

Clinicians should use clinical judgment in considering whether to continue or permanently discontinue treatment. Clinical judgement should take into consideration the individual risk of a subject including the size and location of the cerebral hemorrhage, concomitant anticoagulant use, degree of ARIA-H burden, ApoE ε4 status, and the etiology of the hemorrhage (e.g., hypertensive bleed, spontaneous, trauma) and the possibility of having underlying diagnosis of cerebral amyloid angiopathy.

Given that patients with underlying severe cerebral amyloid angiopathy may have a higher risk of ARIA or cerebral hemorrhage, I recommend that all patients should have a recent baseline MRI prior to initiation of lecanemab to assess for findings such as microhemorrhages, superficial siderosis, cerebral hemorrhage or vasogenic edema, that may suggest underlying cerebral amyloid angiopathy. The safety of lecanemab in patients with history of seizures, TIA or stroke within 12 months prior to study drug initiation, and pretreatment presence of more than 4 microhemorrhages (less than 10 mm at greatest diameter), a single cerebral hemorrhage greater than 10 mm, an area of superficial siderosis, evidence of vasogenic edema, evidence of cerebral contusion, encephalomalacia, aneurysms, vascular malformations, infective lesions, evidence of multiple lacunar infarcts or stroke involving a major vascular territory, severe small vessel, or white matter, disease, space occupying lesions or brain tumors (with the exception of meningiomas or arachnoid cysts which are less than 1 cm at the greatest diameter which are not exclusionary) has not been established.

7.5.2. Cerebral Hemorrhage

Cerebral hemorrhage greater than 1 cm occurring within 40 days after the last dose of study drug, was reported in 0.7% (6/898) of subjects on lecanemab and in no subjects on placebo in 301 Core (excluding a subject on placebo with cerebral hemorrhage occurring more than 60 days after the last dose of placebo and excluding 1 placebo subject identified as having intracranial hemorrhage/temporal lobe hemorrhage with no size indicated). Four of the 6 subjects on lecanemab had cerebral hemorrhage in the setting of ARIA-E or ARIA-H.

Under the treatment emergent cerebral hemorrhage numbers in this review, I included one cerebral hemorrhage on lecanemab occurring 40 days after the last dose of study drug. The reason for this was that this subject ((b) (6) had increase in size of treatment emergent ARIA-E and new ARIA-H 34 days after the last dose of lecanemab, and cerebral hemorrhage occurring 5 days later, suggesting that the cerebral hemorrhage was likely related to the effects of lecanemab. See Section 12.1.9 for the narrative of this subject.

In the labeling, cerebral hemorrhage events > 1 cm inclusive of those occurring beyond 30 days after last dose of study drug were included in both placebo and lecanemab arms, with incidence of 0.1% (1/897) on placebo and 0.7% (6/898) on lecanemab. The purpose of this approach in the label was to demonstrate that cerebral hemorrhage can occur in AD in the absence of treatment with lecanemab.

Three additional subjects, all with placebo exposure in 301 Core, had cerebral hemorrhage greater than 1 cm occurring within 40 days after the last dose of lecanemab in the OLE. One additional cerebral hemorrhage in 301 OLE in the setting of ARIA-E and ARIA-H and 6 days after a biopsy for glioblastoma is not included because it occurred 91 days after the last dose of lecanemab. The incidence of cerebral hemorrhage > 1 cm occurring within 40 days after the last dose of lecanemab in the lecanemab treated subjects 301 Core and OLE combined is 0.6% (9 out of 1612). Use of anticoagulants was associated with an increased risk as discussed in a

presentation of antithrombotic use, under ARIA, above. Two deaths ((b) (6) , (b) (6) were associated with a cerebral hemorrhage as described in Section 7.4.1

In Study 301 Core and OLE, in subjects who had a cerebral hemorrhage greater than 1 cm in diameter, whether symptomatic or not, study drug was temporarily interrupted at the time of the first and second occurrence; however, study drug had to be discontinued after the 3rd occurrence. In 201 OLE study drug was suspended for symptomatic cerebral hemorrhage, but continued dosing was allowed in asymptomatic cerebral hemorrhage.

The observation of non-treatment emergent events, particularly in the subject exposed to placebo, illustrate the difficulty of definitively attributing individual events to lecanemab.

Details of the events of cerebral hemorrhage greater than 1 cm in 301 Core and OLE, including the non-treatment emergent case in the setting of glioblastoma, as well as cerebral hemorrhage during 201 OLE and Study 101 are shown in **Table 80** and in selected narratives in the appendix.

See Section7.4.1 for narratives of subjects (b) (6) and (b) (6) and section 12.1.9 and Table 80 for narratives and descriptions the other subjects in Table 79.

Reviewer Comment: While the number of subjects with cerebral hemorrhage is small, the limited data above suggests that the risk of cerebral hemorrhage on lecanemab is higher compared to placebo. Additionally, in subjects receiving lecanemab, use of antiplatelets increases the risk of cerebral hemorrhage. Incidence of cerebral hemorrhage in subjects on an anticoagulant and lecanemab was 2.5% (2/79) compared to 0/72 subjects on an anticoagulant with placebo. Although the small numbers of events limit definitive conclusions, based on the observed increase in cerebral hemorrhage in subjects on lecanemab, and the increase in the presence of an anticoagulant, I recommend that providers continue to exercise caution when using anticoagulation or thrombolytics in patients receiving lecanemab.

7.5.3. Infusion Related Reactions

Infusion Related Reaction in 301 Core

Consistent with the findings in 201 Core and as described in the currently approved labeling, 236/898 (26%) of subjects on lecanemab experienced one or more infusion related reactions compared to 64/897 (7%) on placebo 301 Core (Table 30). A similar incidence was observed in in 301 Core and OLE combined (24%). The incidence of an infusion related reaction was lower in 301 OLE alone (13%) as most infusion related reactions occurred at the time of the first infusion

Table 30 Incidence of Infusion Related Reactions in 301 Core

	Placebo N=897 n (%)	Lecanemab N=898 n (%)
Infusion Related Reactions	64 (7%)[a]	236 (26%)[a]
Deaths	0	0
Serious Events	0	11 (1)
Discontinuations	1 (0.1)	12 (1)

[a] Does not include 1 AE identified as an infusion site reaction in lecanemab and 2 in placebo.

Please see Section 14.1.3 Table 83 for a summary of serious infusion related reactions, and Section 12.1.10 for narratives of SAEs and discontinuations related to infusion related reactions.

Approximately 76% (179 /236) of the infusion related reactions in subjects receiving lecanemab occurred at the time of the first infusion. The maximum clinical severity of infusion related reactions on lecanemab was mild in 69%, (162 /236), moderate in 28% (67/236), and severe in 3% (7/236). In the placebo arm 86% (55 out of 64) of the infusion related reactions were mild, and none was severe.

In Study 301 Core, one or more infusion interruption due to an infusion related reaction occurred in 1.4% (13 out of 898) of subjects on lecanemab, compared to 0.7% (6 out of 897) of subjects on placebo. Study drug discontinuation due to an infusion related reaction occurred in 1.3% (12 out of 898) of subjects on lecanemab compared to 0.1% (1 out of 897) of subjects on placebo. Of the infusion related reactions leading to study drug discontinuation in the study drug arm, the clinical severity rating was mild in 2, 5 were moderate, and 5 were severe. Six of the reactions leading to discontinuation were serious, all on lecanemab. Please see Section 12.1.10 for narratives and summary of SAEs, and drug discontinuations due to infusion related reactions.

In 301 Core of the 236 subjects who had an infusion related reaction on lecanemab, 94% (221/236) went on to receive more infusions. Forty-four percent (97/221) received one or more preventative medication at subsequent infusions, and 56% (124/221) did not receive preventive medications in subsequent infusions. The most frequently used preventive medications included corticosteroids, antihistamines, and analgesics/antipyretics Of the 236 subjects who had an infusion related reaction while on lecanemab 33.3% (79/236) went on to have one or more infusion related reactions. The incidence of subsequent infusion related reactions on lecanemab after a first event was similar with (37%, 36/97) and without (35%, 43/124) preventive medication. (*Source: Sponsor Tables 14.3.2.6.7 and 14.3.2.6. 8. Submitted in response to an IR from the Agency on April 20, 2023).* The numbers were too small to determine if preventive medications reduced the severity of subsequent infusions.

Symptoms associated with infusion reactions in 301 Core included increased blood pressure (including subject (b) (6) with blood pressure of 180/85 mmHg approximately 4 hours after an infusion and (b) (6) with blood pressure of 190/90 mmHg 2 hours after the first infusion),

increased heart rate and respiratory rate, rigors, chills, fevers, cyanosis, headache, syncope, nausea, and vomiting, similar to those described in Core 201 that included fever and flu-like symptoms (chills, generalized aches, feeling shaky, and joint pain). Some subjects experienced hypotension, hypertension, nausea, vomiting, or desaturation. Serious events are described in Section 12.1.10 Table 83.

Subject (b) (6) had a life-threatening reaction with nausea, vomiting, dyspnea with increased respiratory rate, retraction and wheezing, back stiffness and pain, increased chills and cold extremities, 2 hours after the beginning of the infusion and was treated with epinephrine. This reaction meets the Sampson criteria for an anaphylactic reaction. [22]

After the first dose of study drug in 201 Core, it has been observed that there is a reduction in lymphocyte count and increase in neutrophil count (See Section 7.4.3 Laboratory findings). Those laboratory values were not measured after infusion in 301 Core.

In the 301 OLE alone, the incidence of infusion related reactions was 182/1385 (13%), and for the 301 Core and OLE combined it was 395 (24.5%). See Section 12.1.10 for details of infusion related reaction in the 301 Core and OLE combined.

7.5.4. Hypersensitivity Reactions

301 Core

The incidence of TEAEs belonging to Hypersensitivity SMQ (narrow)[23] was higher in the lecanemab arm compared to placebo (Table 31). This was mainly driven by the increased frequency of infusion related reactions in the lecanemab arms compared to placebo. For example, of the 290 TEAES in the lecanemab arm captured under the Hypersensitivity SMQ narrow, 210 were infusion related reactions. This is similar to the findings in 201 Core.

Table 31 Incidence of a Subject Reporting at Least One Hypersensitivity-Related TEAE in the Placebo-Controlled Period of Study 201 Core.

[22] Sampson HA, Muñoz-Furlong A, Campbell RL, Adkinson NF Jr, Bock SA, Branum A, Brown SG, Camargo CA Jr, Cydulka R, Galli SJ, Gidudu J, Gruchalla RS, Harlor AD Jr, Hepner DL, Lewis LM, Lieberman PL, Metcalfe DD, O'Connor R, Muraro A, Rudman A, Schmitt C, Scherrer D, Simons FE, Thomas S, Wood JP, Decker WW. J Allergy Clin Immunol. 2006;117(2):391.

[23] The Hypersensitivity SMQ Narrow included the following Preferred Terms: SMQ. Preferred Terms captured include allergic cough, application site hypersensitivity, bronchospasm, conjunctivitis allergic, contrast media allergy, dermatitis, dermatitis allergic, dermatitis atopic, dermatitis contact, drug hypersensitivity, eczema, hand dermatitis, hypersensitivity, infusion site rash, injection site rash, lip swelling, periorbital edema, periorbital swelling, rash, rash erythematous, rash pruritic, rhinitis allergic, skin reaction, urticaria, urticarial vasculitis

	Placebo N=897 N(%)	LEC10-BW N=898 (N%)
Hypersensitivity SMQ (Narrow)	125(14)	290(32)
Hypersensitivity SMQ (Narrow), excluding infusion reactions*	65 (7)	80 (9)*
Rash MQG **	37 (4)*	52 (6)

Reviewer created table using the MedDRA Based Adverse Event (MAED) program to analyze the 90-day updated ADAE dataset, selected for , SAFFL=Y, TRTEMFL =Y. and Hypersensitivity SMQ Narrow.
**Mostly driven by the following preferred terms rash , hypersensitivity , dermatitis contact eczema , urticaria, infusion site rash , dermatitis, drug hypersensitivity and pruritic rash all in 2 each.*
***Rash MQG includes the following preferred terms which occurred higher on study drug than placebo: acne, erythema, infusion site rash, injection site rash, rash, , rash erythematous, rash pruritic, skin reactions, and urticaria.*

Excluding infusion related reactions, the following PTs had a higher frequency in the lecanemab arm compared to placebo: rash 3.4% (31 out of 898) vs 2.1% (17 out of 897), hypersensitivity 1.7% (15 out of 898) vs % 0.9 (8 out of 897), dermatitis contact 1.4% (13 out of 898) versus 1.3% (10 out of 897), urticaria 0.6% (5 out of 898) vs 0.3% (3 out of 897), infusion site rash 0.3% (3 out of 898) vs 0 out of 897.

An AE of Hypersensitivity led to study discontinuation in one placebo and one lecanemab-treated subject (b) (6)). This subject had normal vital signs prior to the first infusion. About 3.5 hours after the start of the first infusion, her blood pressure, heart rate and respiratory rate increased slightly compared to baseline, but she remained afebrile. About 4 hours after the start of the first infusion, she experienced nausea and fever (which were symptoms observed with an infusion related reaction in the original BLA review). She was subsequently hospitalized for fever and nausea. In the hospital she was found to have an elevated white blood cell (WBC) count of 10.7 × 103/dL, neutrophils of 94.8%, elevated procalcitonin (PCT) of 5.71 ng/mL, and C-reactive protein of 0.7 mg/dL (normal ranges not reported). That same day (study day 1), the subject was suspected to have sepsis. Urine WBC count was elevated at 50 to 60/high power field and she was started on prophylactic antibiotic therapy with ertapenem 1000 mg IV QD and vancomycin 1000 mg IV BID. Her blood culture, urine culture, and chest x-ray results came back negative. Her symptoms resolved on Day 2 and study drug was discontinued due to serious moderately severe hypersensitivity reaction as well as to a new diagnosis of variable immunodeficiency. There were no other serious hypersensitivity reactions in study 301 Core. Study drug was interrupted due to hypersensitivity in one placebo subject and one subject on lecanemab (b) (6)).

Additionally, the following PTs under the hypersensitivity SMQ Narrow occurred in one subject on the lecanemab arm and were all considered nonserious: lip swelling (b) (6)), periorbital swelling (b) (6), periorbital edema (b) (6)), urticarial vasculitis (b) (6), and bronchospasm ((b) (6)); there was one subject on placebo who also had periorbital edema ((b) (6)). Only one subject ((b) (6)) had a narrative. This subject experienced infraorbital edema that was categorized as mild and nonserious after the 4th dose of study drug, and she was treated with methylprednisolone with complete resolution of symptoms No action was

taken with study drug. This subject continued with study drug without recurrence of symptoms until study day 266 when she withdrew from the study.

Subjects on lecanemab in 301 Core had a higher incidence of a Rash MQG, compared to placebo (5.8% vs 4.1%). This MQG included the following preferred terms which occurred at a higher frequency on lecanemab: acne, erythema, infusion site rash, injection site rash, rash, rash erythematous, rash pruritic, skin reactions, and urticaria.

There were no rash related AEs categorized as serious in 301 Core. In the lecanemab arm, study drug was withdrawn from one subject due to an event of urticaria which was categorized as moderate ((b) (6) in clinical severity and nonserious. This subject received the 6th dose of study drug on study day 71. On study day 72 he experienced urticaria on chest, stomach, arms and legs which was moderate in severity and nonserious. No treatment was reported for this event, but he was permanently discontinued due to this event. Urticaria resolved on study day 79. In three subjects study drug was interrupted for erythema (b) (6)), or rash (b) (6)). There were no subjects on placebo in whom study drug was interrupted or withdrawn due to a rash.

Reviewer Comment: The data above suggest that drug related skin reactions are not uncommon and occur at higher incidence in subjects receiving lecanemab compared to placebo. These skin reactions are mostly mild or moderate and managed without interruption of dosing in most cases.

Reviewer Comment: I recommend that the warning section in the label that currently describes infusion related reactions be revised to also include hypersensitivity reactions, including rash and anaphylaxis as potential risks of study drug.

301 OLE

In the LEC10BW treated population, Core and OLE combined, the incidence of hypersensitivity reaction was 1.2 % (20/1612), with 15 events occurring during the Core and 5 during the OLE. The incidence of Rash MQG was of 5.1 % (82/1612) in the combined Core and OLE period, with 52 occurring during the core, and 30 occurring during the 301 OLE period.

201 OLE

In the 201 OLE study the incidence of infusion related reaction was 21.1% (38 out of 180), and the incidence of rash was 2.8 (5 out of 180). (Table 51)

Of the infusion related reactions in the 201 OLE, one was serious (b) (6)), 5% (2/38) were severe, 58% (22/38) were moderate and 37 % (14/38) were mild.

7.5.5. Seizures

During the 301 Core and OLE, seizures occurred both independent of ARIA as well as related to ARIA.

In 301 Core, the incidence of seizure SMQ narrow was slightly higher on lecanemab compared to placebo, 0.7% (6 out of 898) vs 0.4% (4 out of 897). One subject with a preferred term of drop attacks ([redacted]) was deemed to be a pre-syncopal event unrelated to ARIA was not included in these numbers. One subject [redacted]) who had a cerebral hemorrhage and seizure 40 days after last dose of lecanemab was included in these numbers.

Of the 6 subjects in 301 Core who had a seizure on lecanemab, 3 [redacted] were adjudicated by this reviewer to not be associated with an ARIA or cerebral hemorrhage event. The sponsor adjudicated subject [redacted] as having had a seizure related to ARIA-H. This 73-year-old ApoE ε4 homozygote had a single ARIA-H microhemorrhage identified on study day 192 (23 days after the 13th dose of study drug on study day 169) and remained asymptomatic. On study day 213 (two days after the 15th dose of study rug), she experienced a fever, syncope and two possible seizures. She was taken to the ER where she was found to have diarrhea and shivering, and ultimately diagnosed with diverticulitis and COVID 19. In this case the seizure does not appear to be related to ARIA-H or study drug.

Three subjects on lecanemab in 301 Core were adjudicated by this reviewer to have seizures in the setting of ARIA ([redacted]), or cerebral hemorrhage [redacted]).

Three subjects on placebo [redacted]) had a seizure not associated with ARIA or cerebral hemorrhage, and one subject who had a seizure associated with ARIA-E or ARIA-H [redacted]

Based on a data cutoff of December 1, 2022, in study 301 OLE, 13 subjects had a seizure while on lecanemab. Of these, 6/1315 [redacted]) occurred in the setting of ARIA, and one in the setting of cerebral hemorrhage ([redacted] Six subjects (6/1315, 0.4%) had a seizure ([redacted] which was not associated with ARIA-E or ARIA-H.

ARIA related seizure events are described under Section 12.1.9 for details.

7.5.6. Suicide Risk

I did not identify a higher risk of suicidal ideation in those receiving lecanemab compared to placebo

In 301 Core, at baseline there was one subject on placebo and none on lecanemab that had an affirmative response to suicidal behavior. During 301 Core, there was one treatment emergent

suicidal behavior (0.1% ,1/898) subject (b) (6) on lecanemab and none on placebo. See Section 12.1.4 for his narrative.

In Study 301 Core, the incidence of one or more treatment emergent affirmative responses on the C-SSRS related to suicidal ideation was 1.7% (15/898) on lecanemab and 2.7% (24/897) on placebo. Additionally, there were two subjects on lecanemab who had an affirmative response to non-suicidal self-injurious behavior.

In Study 301 OLE the incidence of one or more treatment emergent affirmative response on the C-SSRS related to suicidal ideation was 0.1% (2/1385). In 301 OLE. There was one subject on lecanemab who had an affirmative response to non-suicidal self-injurious behavior. There was no subject with an affirmative response to suicidal behavior in the 301 OLE.

In 301 Core, 1 subject on lecanemab (b) (6)) and 4 on placebo had a TEAE of suicidal ideation. Intentional self-harm occurred in one subject (b) (6)) during 301 Core as described above. In 301 OLE, there was 1 subject (b) (6)) with a TEAE of suicide attempt. Additionally, in 301 Core, there were 3 subjects (b) (6)) who had a TEAE of suicidal ideation.

The narratives for subjects (b) (6) and (b) (6) are described in See Section 12.1.4

Reviewer Comment: Two of these subjects did not have a history of suicidal ideation or a past medical history of depression ((b) (6)), and 4 either had a past medical history of depression, or positive answers to suicidal ideation at screening or baseline (b) (6)). Given the small number of subjects, some of which had a history of depression or suicidal ideation prior to initiation of study drug, I cannot conclusively determine a role of study drug in these instances.

7.6. Safety Analyses by Demographic Subgroups

I evaluated the TEAES reported in the 301 Core study by the following demographic parameters: sex, age group, race, region, BMI, and baseline diagnosis (MCI vs AD). Overall, there were no major differences in the incidence of ARIA-E and ARIA-H between sex, age (< 65 years and ≥ 65 years old), or baseline diagnosis. (Table 32). The incidence of ARIA-E was lowest in patients at least 80 years old; the inflammatory response against amyloid may not be as robust in that age group. However, any noted differences in race, age > 80 years and BMI may be limited by the small numbers in these subgroups.

There were additional TEAEs that had different incidence in different subgroups, such as headache shown in Table 32, and other TEAEs not included in Table 32. The small number in most of these subgroup analyses excluded any firm conclusions about the significance of these differences.

Table 32 Incidence of Most Common TEAEs on Lecanemab by Subgroups

Lecanemab Arm	ARIA-E	ARIA-H	Headache	Infusion Related Reaction	Overall TEAEs
Males (n=436)	12%	15%	9%	28%	90%
Females (n=462)	13%	13%	13%	24%	80%
<65 years old (n=175)	14%	9%	14%	24%	87%
65-80 years old (n=593)	14%	16%	12%	27%	90%
At least 80 years old (n=130)	5%	13%	5%	27%	88.5%
White (n=685)	14%	15%	13%	28%	90%
African American (n=22)	9%	14%	9%	9%	86%
Asian (n=153)	6.5%	10.5%	5%	12%	84%
Other (including missing) (n=38)	21%	18%	16%	67%	97%
MCI (n=552)	13%	14%	12%	26%	88%
AD (n=346)	12%	14.5%	10%	27%	90%
North America (n=537)	13%	14.5%	11%	29%	89%
Europe (n=215)	15%	15%	17%	29%	94%
Asia Pacific (n=146)	6%	10%	4%	12%	84%
BMI< 22.5 (n=212)	9%	9%	8%	18%	86%
BMI 22.5-24.9 (n=194)	13%	13%	12%	39%	90%
BMI 24.9-27.9 (n=222)	11%	17%	11%	28%	88%
BMI at least 27.9 (n=268)	15%	16%	13%	36%	91%

7.7. Specific Safety Studies/Clinical Trials

Not Applicable

7.8. Additional Safety Explorations

7.8.1. Human Carcinogenicity or Tumor Development

The SOC Neoplasm had a higher incidence in those on lecanemab 8.6% (77/898), compared to placebo 6.5% (58/897). There were 8 PTs falling under the SOC of Neoplasm that showed a higher frequency on lecanemab compared to placebo (Table 33).

Mean exposure (SD) to the study drug in months in 301 Core study was 15.7 (SD 5.0, range: 0.5-18.8) on lecanemab and 16.5 (SD 3.9, range 0.5-20) on placebo. (Source: Applicant Table 9, Study 301 Core CSR)

Mean exposure (SD) in months to lecanemab in the combined Core and OLE period for the 1612 subjects, was 17.4 (SD 10.83, range 0.5-42) months (Source: Applicant Table 14.3.1.1.1 301 OLE CSR). In the 714 subjects who were new exposures to lecanemab in 301 OLE, the mean (SD) exposure in months to lecanemab was 9.6 (SD 5.3, range 0.5-23) (Source: Applicant Table 14.3.1.1.2 301 OLE CSR).

The risk difference between lecanemab and placebo in the occurrence of the neoplasms which occurred at a higher incidence on lecanemab ranged between 0.1% -0.6%, and the significance of these findings is unclear.

Table 33 TEAES Belonging to the SOC of Neoplasm Occurring in 2 or More Subjects on Lecanemab and at a Higher Frequency than Placebo

Preferred Term	Placebo N=897 N(%)	Lecanemab N=898 N(%)
Basal cell carcinoma	10 (1.1)	15(1.7)
Squamous cell carcinoma of skin/squamous cell carcinoma/squamous cell carcinoma oral cavity	10 (1.1)	13(1.5%)
Breast cancer/breast cancer in situ/invasive ductal breast cancer/breast cancer in situ, intraductal proliferative breast lesion, breast neoplasm, fibroadenoma of breast	3(0.3)	6(0.7)
Lipoma/spinal cord lipoma	0	5(0.6)
Skin papilloma	0	3 (0.3)
External ear neoplasm malignant	1(0.1)	2(0.2)

Source: ADAE dataset: reviewer created May 18, 2023.

In Study 301 OLE the incidence of a subject experiencing a TEAE within the SOC Neoplasm was 3.8% (53/1385).

Table 34 Treatment Emergent Adverse Events Belonging to the SOC of Neoplasm in 2 or More Subjects in 301 OLE

Neoplasms benign, malignant and unspecified (incl cysts and polyps)	N=1385 N(%)
Basal Cell Carcinoma	16
Seborrheic keratosis	8
Squamous cell carcinoma	6
Skin papilloma	3
Lipoma	2
Prostatic adenoma	2
Skin Cancer	2

I note that there have been two subjects in the lecanemab clinical development program who were diagnosed with a primary brain tumor of glioblastoma after exposure to lecanemab. Subject (b) (6) is an 81-year-old female with who received lecanemab 2.5 mg/kg IV once every two weeks in the 201 core study. After receiving the 32nd dose of study drug (after an exposure of one year and 2 months), the safety MRI showed an area of vasogenic edema in the anterior left temporal lobe. On serial safety MRIs over time, an enhancing ring lesion suspicious for an underlying neoplasm became evident. The subject ultimately died, and the autopsy showed a high-grade infiltrating astrocytic neoplasm.

Subject (b) (6), a 72-year-old white male, was randomized to placebo in 301 Core. This

subject received 27 doses of lecanemab during the OLE (~ 1 year of exposure). On extension day 352, the day of the last dose, study MRI showed a space occupying lesion in the left parietal region. On extension Day 411, a single new ARIA-H microhemorrhage, and 10mm superficial siderosis were also noted in the left parietal region, and a 10mm superficial siderosis I the same area. On extension day 435, the subject was hospitalized and underwent a biopsy, which confirmed a Grade 4 glioblastoma. On extension day 442, the subject experienced a cerebral hemorrhage > 1 cm in the left occipital region.

Reviewer Comment: It is difficult to ascertain whether the study drug played a role in these events of glioblastoma. The duration of exposure of ~ 1 year is relatively short for malignancies. Neither of the patients had previous radiation exposure. One subject is a male over 50 years of age which is a known risk factor. Some epidemiological studies suggest a positive correlation between AD and glioma, although there are some limitations to these studies.[24]

7.8.2. Human Reproduction and Pregnancy

There is no safety data on the use of lecanemab in pregnant women. The applicant notes that no pregnancies have been reported in any clinical study of lecanemab.

7.8.3. Pediatrics and Assessment of Effects on Growth

Not applicable.

7.8.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Overall, I did not identify a safety signal for abuse potential, withdrawal or rebound in a search of TEAEs related to abuse potential.

In 301 Core and OLE combined, there were two subjects ((b) (6) with accidental overdose with lecanemab. One had a narrative (b) (6)) and no adverse reactions were reported. The AE dataset reports headache the day after the accidental overdose. In subject (b) (6) no narrative related to the overdose was provided, and the AE dataset did not report any AEs around the time of the overdose.

I searched for TEAEs related to abuse potential identified in the Guidance for Industry, "Assessment of Abuse Potential of Drugs".[25] I did not identify a signal for abuse related

[24] Mokbul IM, Siddik AB. Relationship between glioblastoma multiforme (GBM) and Alzheimer's disease (AD): is there any reporting bias? Med Oncol. 2023 Feb 21;40(3):101. doi: 10.1007/s12032-023-01951-9
[25] The following preferred terms were used: abnormal behavior, abnormal dreams; apathy; affect lability, aggression, agitation, confusional state, delusion, delusional disorder, depersonalization/derealization disorder;

potential in 301 Core.

To assess for withdrawal and rebound, I evaluated the TEAEs occurring in subjects during the follow up period, occurring after 14 days after the last dose of study drug. Of these TEAEs only ARIA-H occurred at 2% frequency on lecanemab and 2% higher than placebo suggesting that there was not a consistent pattern of TEAES associated with withdrawal and rebound occurring at a higher frequency on lecanemab.

7.9. Safety in the Postmarketing Setting

7.9.1. Safety Concerns Identified Through Postmarketing Experience

The first periodic safety update for the period covering January 6, 2023, to April 5, 2023, did not identify any new safety signals.

7.9.2. Expectations on Safety in the Postmarketing Setting

As part of the postmarketing pharmacovigilance requested at the time of the Accelerated Approval of the original BLA submission, the Applicant was asked to send all fatal reports, including not related clinical trial fatal reports, and 15-day reports of serious events to BLA 761269. Any fatal reports that meet IND reporting requirements were also to be submitted to IND 105081. The Applicant was also to provide biannual reports of ARIA-E and ARIA-H (specifying microhemorrhage or superficial siderosis), along with any incident cerebral hemorrhage greater than 1 cm in size.

7.9.3. Additional Safety Issues From Other Disciplines

The reader is referred to the OCP review of risks associated with immunogenicity.

7.10. Integrated Assessment of Safety

The most common adverse drug reactions with lecanemab are infusion-related reactions, ARIA-H, ARIA-E, and headache. All occurred in at least 10% of subjects on lecanemab and at least 2% more frequently than placebo in the controlled period of Study 301. This was consistent with the most common adverse reactions observed in Study 201 Core.

While only 3% of ARIA was symptomatic in study 301 Core, serious and life threatening

dizziness, dysphoria; euphoric mood; feeling abnormal, feeling drunk; hallucination; hallucination visual; hallucination auditory; illusion; mental impairment, mental status change, mood swings, and somnolence

events, including a fatal event in a patient with severe ARIA-E in 301 OLE, have occurred. Serious intracerebral hemorrhage, some of which have been fatal, have been observed in patients treated with Lecanemab.

Risk management for ARIA and cerebral hemorrhage can be achieved through clear product labeling and monitoring for ARIA, as described in the label.

Infusion-related reactions occurring in the controlled trial were moderate or mild, primarily occurring with first dose, and subsequently prevented in some cases by pre-treatment. Infusion reactions are included in Warnings and Precautions in the currently approved label. Hypersensitivity reactions, including angioedema and anaphylaxis will be added in Warnings and Precautions, with a contraindication in patients with serious hypersensitivity to lecanemab. There are no safety issues that preclude approval.

Safety findings from BLA 761178 are summarized below.

Deaths: In Study 301 CORE, there was not an excess of deaths in the lecanemab-treated group (0/7%) compared to placebo 0.8%)for deaths for which the precipitating event occurred within 30 days after the last dose, and excluding two deaths which occurred more than 30 days after last study treatment administration, one each on placebo and lecanemab) (Table 6). As of a 90-day data cutoff date of December 1, 2022, there were 9 deaths during the 301 OLE, in 2 of which the study drug may have played a role.

Serious Adverse Events: In the placebo-controlled Study 301 Core, treatment emergent serious adverse events (SAEs) occurred in 14% (126/898) of lecanemab-treated subjects and in 11% (101/897) of placebo-treated subjects. The system organ class (SOC) categories with the highest incidence of SAEs in the lecanemab arm and greater than placebo were injury, poisoning and procedural complications (3%, driven by infusion reactions) and nervous system disorders (3%, driven by ARIA-E and syncope), followed by cardiac disorders (2%) and infections and infestations (2%).

Discontinuations: In 301 Core, 22% of subjects receiving the study drug discontinued study treatment compared to 17% on placebo. During the 301 Core discontinuations from study treatment due to adverse events occurred in 7% of subjects receiving study drug compared to 3 % on placebo. In the 301 core study the most frequently reported TEAEs leading to treatment discontinuation by primary organ system were: nervous system disorders, and injury, poisoning and procedural complications. The most frequently reported preferred terms that led to discontinuation were ARIA-H, ARIA-e, and infusion related reaction.

Significant AEs: Overall, in 301 Core the evaluation of significant AEs did not identify a new safety signal. Most TEAEs were mild or moderate, with approximately 7 % considered severe in both the lecanemab and placebo arms. The preferred terms for the severe AEs with the highest frequency on lecanemab vs placebo were infusion related reaction (0.8% vs 0), fall (0.4% vs 0.2%), and ARIA-E (0.3% vs 0).

Most common TEAEs: The most common TEAEs occurring in at least 5% of subjects in the lecanemab arm compared to placebo in 301 Core were infusion related reactions, ARIA-H, ARIA-E and headache, all already established during the initial review and currently listed in the Leqembi label. Additionally, an FDA MQG rash, superficial siderosis and nausea and vomiting were identified.

Laboratory: During the original submission, the main finding related to laboratory assessments in Study 201 Core was that those receiving lecanemab were more likely to experience a transient decrease in lymphocytes, and an increase in neutrophils after the first infusion. Because in 301 Core blood collection only occurred prior to the infusion, whether there is a reduction in lymphocyte count and increase in neutrophils immediately after an infusion could not be assessed with this supplemental submission. Overall, in Study 301 Core, there were no clear trends or differences in hematology, chemistry or liver values between the placebo and lecanemab groups. Similar to observations in 201 Core, there was a higher incidence of hematuria on lecanemab 2.3% (21/898) vs 0.7% (7/898) on placebo.

Hepatic Safety: – There was no signal of hepatotoxicity identified. There was one subject on placebo, and no subjects on lecanemab who met Hy's Law criteria

Vital sign evaluations: When examining shifts from baseline to abnormal vital signs, the following appeared to have occurred at ≥ 2% frequency on lecanemab and at a higher frequency that with placebo: pulse rate >100, respiratory rate <12, respiratory rate >20, and weight decrease ≥7% from baseline (Table 18) The clinical significance of these findings is not clear.

ECG Evaluations: Overall I did not identify a clinically meaningful difference in changes in ECG measures during the course of 301 Core in subjects on lecanemab compared to placebo. Similarly, I did not identify a persistent trend in shifts to abnormal clinically significant, or abnormal clinically nonsignificant ECGs in the proposed dose arm compared to placebo. There was a higher incidence of TEAE of atrial fibrillation and atrial flutter on lecanemab versus placebo (2.8% vs 1.6%) and a higher incidence of a TEAE of QT prolongation in the lecanemab arm compared to placebo (0.7% vs 0).

Immunogenicity: As noted in the original review, the ADA assay used by the applicant was not reliable for accurate classification of ADA status, due to interference by serum lecanemab concentrations, possibly resulting in an underestimation of the incidence of antibody formation. As a result, no comparisons could be conclusively made in the incidence of TEAEs in ADA negative vs positive subjects. Postmarketing requirements (4384-2 and 4384-3) were imposed with the January 6, 2023, accelerated approval, to improve the assay sensitivity and to use the improved and validated assay to assess the impact of antibody formation on pharmacokinetics, pharmacodynamics, safety, and efficacy of lecanemab in patients enrolled in the confirmatory study. In their review of S-001, OCP and OPB concluded that the assay

remains inadequate for this purpose. The impact of immunogenicity on pharmacokinetics, pharmacodynamics, efficacy, and safety will be evaluated when data to support the postmarketing requirements (PMRs) are submitted.

Adverse Events in Subjects Without ARIA: The most common TEAE in those without ARIA were infusion related reactions.

Suicidality: There was no evidence of an increased risk of suicidality on lecanemab.

ARIA: The overall incidence of ARIA in 301 Core, 21% on lecanemab and 9 % on placebo, is higher than that observed in 201 Core where ARIA occurred in 12% on lecanemab and 5% on placebo. In 301 Core on lecanemab, the risk of ARIA-E was highest in ApoE homozygotes (33%), followed by heterozygotes (19%), and noncarriers (5%). Risk of ARIA-H showed a similar pattern. In patients on lecanemab the majority of ARIA cases in 301 Core were asymptomatic, similar to the findings in 201 Core in the original BLA. In Study 301 Core, symptomatic ARIA occurred in 29 out of 898 (3%) of subjects treated with lecanemab compared to 2 out of 897 (0.2%) on placebo. In 301 Core, 3% of patients treated with lecanemab had symptomatic ARIA-E and 1% had symptomatic ARIA-H. The most common symptom observed in patients with ARIA-E was headache (12/898, 1%); other reported symptoms included confusional state, dizziness, nausea, combination of different visual changes, other focal neurologic deficits, and seizure. In 301 Core in those on lecanemab, 72% (81/113) of ARIA-E events occurred prior to the 7th dose and on average lasted for 92 days (range 16-374).

The label should continue to include Warnings about ARIA and instructions for ARIA monitoring and management. Because cerebral hemorrhage greater than 1 cm has been observed in patients taking lecanemab, a statement recommending that prescribers exercise caution when prescribing concomitant antithrombotics or thrombolytics should remain in the Warnings and Precautions section of the label.

Hypersensitivity Reactions: There was a higher incidence of TEAEs belonging to Hypersensitivity SMQ (narrow), in the lecanemab arms compared to placebo. This was mainly driven by the increased frequency of infusion related reactions on lecanemab compared to placebo. The incidence of having a Rash MQG was 6% on lecanemab and 4% on placebo. One subject at the proposed dose arm had anaphylaxis after an infusion, and one subject experienced urticaria that led to study drug discontinuation.

Infusion Related Reactions. The incidence of infusion related reactions was 26% on lecanemab and 7% on placebo. Most were mild or moderate in severity. Symptoms associated with infusion reactions in 301 Core included increased blood pressure, increased heart rate and respiratory rate, rigors, chills, fevers, cyanosis, headache, syncope, nausea, and vomiting, similar to those described in Core 201 that included fever and flu-like symptoms (chills, generalized aches, feeling shaky, and joint pain). Some subjects experienced hypotension, hypertension, nausea, vomiting, or desaturation. Some subjects received preventive medications in subsequent infusions. Infusion related reactions were treated with nonsteroidal

anti-inflammatory, analgesic/ antipyretic, antiemetics, antihistamines or corticosteroids. The incidence of repeated infusion related reactions appeared to be similar in those who received preventive medications compared to those who did not.

8. Advisory Committee Meeting and Other External Consultations

An Advisory Committee meeting was held on June 9, 2023. The Advisory Committee was asked to comment on the following:

- Discuss the results from Study 301 (CLARITY AD) and whether they provide evidence of clinical benefit of lecanemab for the treatment of Alzheimer's disease (AD).
    - Vote: Do the results of Study 301 (CLARITY AD) verify the clinical benefit of lecanemab for the treatment of AD?

    The Advisory Committee members unanimously agreed that the data confirm the clinical benefit of lecanemab for the treatment of AD.

- Discuss the overall benefit/risk assessment of lecanemab for the treatment of AD.

    The AC Committee members agreed that the overall benefit/risk assessment appeared favorable.

- Additionally, consider the following subgroups in your assessment:
    - Apolipoprotein E (ApoE) ε4 homozygotes

The committee noted that language regarding recommendations for ApoE genotyping to inform risk should be stronger in labeling.

    - Patients requiring concomitant treatment with anticoagulant agents

The AC Committee members were divided as to whether patients should be treated with concomitant anticoagulants and lecanemab. More panelists favored not excluding patients taking anticoagulants from treatment with lecanemab, allowing for clinical judgement of the prescriber based on individual evaluation.

    - Patients with cerebral amyloid angiopathy

The panel noted that it would be difficult to exclude patients for a condition that does not have definitive clinical diagnostic criteria. However, it was noted that the potential risk with CAA could be more clearly stated in the label which could then help inform prescribers and patients about potential risks.

9. Labeling Recommendations

9.1. Prescription Drug Labeling

A Boxed Warning will be added to the label to inform the prescriber of the risk of ARIA and cerebral hemorrhage as well as the increased risk observed in ApoE ε4 homozygotes, and to state that ApoE ε4 status should be obtained prior to initiation of treatment with lecanemab to inform the risk of developing ARIA.

A Warnings and Precautions Section 5.1 of the currently approved Prescribing Information alerts prescribers to the risk of ARIA and cerebral hemorrhage. Language has been added to note that patients who may be at increased risk for intracranial hemorrhage, including those with findings suggestive of CAA were excluded from the clinical trials, that the presence of ApoE ε4 alleles is associated with CAA, and that caution should be exercised when considering the use of lecanemab in patients with factors that indicate an increased risk for intracerebral hemorrhage, and in particular for patients who need to be on anticoagulant. Information regarding ARIA is also addressed in the Medication Guide. Guidance regarding monitoring and implications regarding a finding of ARIA on subsequent dosing is provided in Sections 2.3 and 5.1 of the prescribing information.

The currently approved label includes Warnings and Precautions that makes prescribers aware of the risk of infusion related reactions. Hypersensitivity reactions, including angioedema, bronchospasm, and anaphylaxis will be added to Warnings and Precautions, with a contraindication in patients with serious hypersensitivity to lecanemab or to any of the excipients. This will also be addressed in the Medication Guide.

9.2. Nonprescription Drug Labeling

Not applicable

10. Risk Evaluation and Mitigation Strategies (REMS)

The Agency has determined that there is not a need for a REMS.

11. Postmarketing Requirements and Commitments

Post-marketing enhanced pharmacovigilance was specified in the initial accelerated approval letter and will remain in effect.

The following PMRs will be imposed for BLA 761269 S-001:

1) A registry-based, prospective, observational study to evaluate clinical safety outcomes among AD patients treated with lecanemab, using, for example, the Alzheimer's Network for Treatment and Diagnostics (ALZ-NET) registry.
2) A study to validate administrative claim codes and use those codes to evaluate clinical safety outcomes of interest in a retrospective cohort study.
3) A trial to further characterize the safety lecanemab in patients who are homozygous for ApoE ε4.

The following PMC will be issued:

Validation testing for an FDA cleared or approved in vitro diagnostic device to accurately and reliably detect ApoE e4 alleles.

12. Appendices

12.1.1. Schedule of Assessments for Study 301

Table 35 Schedule of Assessments for 301 Core

Sponsor Table 9 Schedule of Procedures/Assessments BAN2401-G000-301: Randomization Phase (Visit 3 Through Visit 27 [Week 1 Through Week 49]) (revised per Amendments 05, 06, and 08)

Phase	Randomization																								
Period	Treatment																								
Visit[a,b]	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27
Week	1	3	5	7	9	11	13	15	17	19	21	23	25	27	29	31	33	35	37	39	41	43	45	47	49
Procedures/Assessments																									
Vital signs[c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Weight	X[d]					X[e]	X[d]						X[e]	X[d]					X[e]	X[d]					
Routine physical examination[f]					X				X					X						X					
12-lead ECG					X				X					X						X					
Urine pregnancy test[g]							X							X						X					
Blood for laboratory tests[h]	X	X		X			X							X						X					
Urinalysis	X	X		X			X							X						X					
MMSE[i]							X							X						X					
CDR[i]							X							X						X					
ADAS-Cog14[i]							X							X						X					
EQ-5D-5L[i,j]														X											
QOL-AD[i,j]														X											
ADCS MCI-ADL[i,j]														X											
Zarit Burden Interview[i,j]														X											
C-SSRS[i]	X													X											
Safety MRI[k]					X		X							X											
Volumetric MRI (for PD)[l]					X		X							X											
Amyloid PET[m]							X							X											

Sponsor Table 9 Schedule of Procedures/Assessments BAN2401-G000-301: Randomization Phase (Visit 3 Through Visit 27 [Week 1 Through Week 49]) (revised per Amendments 05, 06, and 08)

Phase	Randomization																								
Period	Treatment																								
Visit[a,b]	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27
Week	1	3	5	7	9	11	13	15	17	19	21	23	25	27	29	31	33	35	37	39	41	43	45	47	49
Procedures/Assessments																									
Randomization	X																								
Study drug administration[n,o]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood for serum BAN2401 PK[p]	X		X				X							X						X					
Blood for serum anti-BAN2401 ADA[q]	X		X				X							X						X					
Blood For Exploratory PD Analysis[r]	X													X											
CSF sampling (PD, PK)																									
Prior/concomitant meds	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Source: Sponsor Table 9, Protocol ban2401-g00-301 protocol version FINAL v11.0: 08 Jun 2022

ADA = antidrug antibody, ADAS-Cog14 = Alzheimer's Disease Assessment Scale-Cognitive subscale 14, ADCS MCI-ADL = Alzheimer's Disease Cooperative
Study-Activities of Daily Living Scale for Mild Cognitive Impairment, AE = adverse event, CDR = Clinical Dementia Rating, COVID-19 = Coronavirus Disease 2019,
CSF = cerebrospinal fluid, C-SSRS = Columbia-Suicide Severity Rating Scale, EQ-5D = European Quality of Life – 5 Dimensions, EQ-5D 5L = European Quality of Life–5 Dimensions 5 Level version, LP = lumbar puncture, MMSE = Mini-Mental State Examination, MRI = magnetic resonance imaging, PD = pharmacodynamic, PET = positron emission tomography, PK = pharmacokinetic, QOL-AD = Quality of Life in Alzheimer's Disease

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a: Assessments should take place on the first day of the study visit in the designated study week except as noted below (footnotes k, l, and m, pertaining to imaging assessments). A visit window of ± 8 days will be allowed for each visit, except for Visit 3; however, there must be at least 7 days between 2 infusion visits. Visit assessments may be split over 2 consecutive days, if needed. This applies to all visits. All clinical and cognitive assessments (eg, cognitive and suicidality scales) must be completed in the prespecified order on the first day of a split visit, before collection of ECG and other assessments. ECG and other assessments can be performed either on the first or the second day of a split visit, always before infusion. Vital signs should be measured, and laboratory samples should be collected on the second day, both before infusion. Note that PK samples are also required predose and following infusion. (revised per Amendments 04 and 08)

b: If under extenuating circumstances (eg, the COVID-19 pandemic), a subject is not able to visit the study site for scheduled safety and efficacy assessments, and the assessment(s) is/are not performed during the respective scheduled visit(s), the assessment(s) should be performed as soon as possible, either as a scheduled visit or as an unscheduled visit unless the next scheduled assessment (s) is (are) expected to occur within 30 days. (revised per Amendment 06)

c: Vital signs will be measured both at predose and after infusion. During Visits 3, 4, 5, and 6, vital signs should be recorded at least 2 hours after study drug infusion, in addition to predose. If at those visits no untoward effects of infusion on vital signs are detected ≥2 hours after infusion, these assessments at subsequent study visits may be conducted at a shorter interval after infusion. At visits where no infusion takes

place (eg, Visit 43), vital signs will be measured once. Vital sign measurements will consist of systolic and diastolic blood pressure (mmHg) measured after at least 3 minutes in a semi-supine position, pulse (beats per minute), respiratory rate (per minute), and body temperature (in centigrade). (revised per Amendment 01)

d: Weight will be taken in the clinic at designated visits. If a subject misses a clinic visit where weight is to be collected, subsequent visits should use the most recent, previous collected weight for infusion calculations until the next clinic visit. Under such circumstances, weight is to be taken at the next clinic visit and entered into the IxRS even if the visit is not designated for weight data collection.

e: Only subjects receiving home infusion at Visits 9, 16, and 22 (during extenuating circumstances, eg, COVID-19 pandemic), will have weight measurement collected at Visits 8, 15, and 21. (revised per Amendment 06)

f: For subjects receiving home infusion at visits where a routine physical examination is scheduled, a symptom-directed physical examination may be performed at the discretion of the investigator if a routine physical examination is not feasible. (revised per Amendment 06)

g: Females of childbearing potential only.

h: Blood for laboratory tests will be taken predose at all visits as indicated.

i: Scales are to be completed in the morning (or, if not possible, consistently at approximately the same time of day) in the following order on the days indicated: MMSE, CDR-SB, and ADAS-Cog14. For any given subject, every effort should be made to ensure that the raters for the CDR, MMSE, and ADAS-Cog14 remain unchanged throughout the study. The clinician responsible for CDR assessment must not participate in the medical management of the subjects and must be blinded to results of all safety assessments (including but not limited to results of safety MRI and clinical laboratory assessments, and AEs), except for the results of the C-SSRS. Every effort should be made to keep the site staff responsible for reviewing laboratory reports (including MRI reports) and assessing AEs separate from the site staff responsible for the MMSE and ADAS-Cog14. The EQ-5D-5L, QOL-AD, ADCS MCI-ADL, and Zarit Burden Interview will be administered after the completion of the ADAS-Cog14. Subjects and study partners (defined as a person able to support the subject for the duration of the study) need to be available in person for these assessments. However, under extenuating circumstances only, and only with the approval of the sponsor (eg, during the COVID-19 pandemic), the MMSE, CDR, ADAS-Cog14, ADCS

MCI-ADL, and C-SSRS may be administered remotely via a sponsor-approved telehealth system for subjects receiving home infusion during the Randomization Phase. For subjects who are unable to travel to the study site during extenuating circumstances and home infusion is not an option, only the CDR, ADCS MCI-ADL, and

C-SSRS may be administered remotely via telephone or via a sponsor-approved telehealth system. (revised per Amendments 01, 04, and 06)

j: At each visit: 3 copies of the EQ-5D-5L will be completed (Subject regarding Self [Standard Version], Partner regarding Subject [Version labeled: Proxy 1], Partner regarding Self [Standard Version], 2 copies of the QOL-AD will be completed (Subject regarding Self [Standard Version], Partner regarding Subject [Version labeled: Proxy]), 1 copy of the ADCS MCI-ADL will be completed (Partner regarding Subject), and 1 copy of the Zarit Burden Interview will be completed (Partner regarding Self [Standard Version]). All "Standard Version" questionnaires will not be labeled with those words, but they will lack a Proxy label. The subject and the subject's study partner must be available in person for these assessments. See footnote i for assessment of the ADCS MCI-ADL during the COVID-19 pandemic and other extenuating circumstances. (revised per Amendment 06)

k: MRI imaging should be conducted at any time following the completion of the immediately preceding visit and prior to each of the following visits according the Schedule of Procedures/Assessments: Visits 7, 9, 16, 29, and 42 and at the Follow-up Visit (Visit 43). In all cases, the safety MRI must be reviewed by the imaging vendor and a local reader prior to a subject receiving the next dose of study drug. In the event of an unscheduled visit, the investigator in consultation with the sponsor will determine whether or not a safety MRI should be conducted. If an Early Termination Visit takes place, an MRI is to be conducted, if not already performed during the preceding 90 days. (revised per Amendment 01)

l: A volumetric MRI sequence will be collected in all subjects immediately following all safety MRI assessments. Volumetric MRI data will be analyzed at the Screening Visit (Baseline) and at 6, 12, and 18 months of treatment.

m: In the amyloid PET substudy only, amyloid PET imaging will be conducted on or within 10 days after the scheduled visits. Subjects who consent to participate in the amyloid PET substudy and who discontinue from the study drug will undergo an amyloid PET as part of the early termination visit only if the preceding amyloid PET assessment was performed 3 or more months before the Early Termination Visit. (revised per Amendment 01)

n: At Visit 3 (Week 1), subjects must stay in clinic for full 4 hours following infusion for safety observation during this first infusion visit. Subjects must stay in clinic for at least 2 hours following infusion up through Week 13 (Visit 9) for safety observation. After the Week 13 (Visit 9) Visit, if no untoward effects of infusion are noted, or infusion reactions can be prevented with prophylaxis, then subjects may be discharged from clinic 30 minutes after the end of infusion if judged medically stable by the investigator. (revised per Amendment 06)

o: If approved by the sponsor and allowable and conducted according to country and local guidelines, subjects may be offered the option of home infusions for all visits except for Visits 3, 9, 16, and 22. However, under extenuating circumstances only, and only with the approval of the sponsor (eg, during COVID-19 pandemic), home infusion at Visits 9, 16, and 22 may be permitted. Home infusion will not be allowed for Visit 3. If home infusion occurs at Visits 4 through 9, subjects must be observed for at least 2 hours following infusion by the infusion staff. After the Week 13 (Visit 9) Visit, if no untoward effects of infusion are noted, or infusion reactions can be prevented with prophylaxis, then subjects will be observed 30 minutes after the end of infusion if judged medically stable by the investigator. For subjects missing 3 or more consecutive doses, and who have not had any safety assessments performed either in-clinic or at the home infusion visit(s) during the period of dose interruption, the following safety assessments must be performed before resuming study drug dosing: AE and concomitant medication

assessments, vital signs, weight, routine physical (where feasible) or symptom directed physical (if routine physical is not feasible), clinical laboratory assessments, C-SSRS, and ECG. Study drug dosing may resume on the same day as these assessments (ie, before receipt of the clinical laboratory assessments results) based on the clinical judgement of the investigator. All laboratory results should be promptly evaluated by the investigator before the subsequent visit to ensure safety of continued study drug dosing. If ECG or clinical laboratory assessments cannot be conducted before restarting study drug dosing, study drug dosing may resume based on the clinical judgement of the investigator. However, these assessments must be performed as soon as possible and results should be promptly evaluated by the investigator before subsequent visits to ensure safety of continued study drug dosing. (revised per Amendment 06)

p: At Visit 3 (Week 1), blood will be taken for the BAN2401 assay approximately 4 hours after the end of infusion (before subjects leave the clinic for home) and subjects must stay in clinic for the full 4 hours following infusion during this first infusion visit for safety observation At Visits 5, 9, 16, and 22, blood will be taken for the BAN2401 assay both predose and at least 2 hours after the end of infusion. If study drug is administered at the study site, subjects are required to remain in clinic for safety observation for at least 2 hours following infusion at visits where PK samples are taken (except Visit 3, the first infusion visit); PK samples will be taken at predose and at any time after 2 hours and should be taken just before the subject leaves the site. If the study drug is administered at a location other than the study site (eg, subject's home), the infusion staff may collect the PK samples any time after 2 hours. (revised per Amendments 01 and 06)q: Blood for the BAN2401 antidrug antibody assay will be taken predose at all indicated visits.

r: Blood for plasma isolation for exploratory biomarker assessments will be taken at predose. (revised per Amendments 01 and 04)

Table 10 Schedule of Procedures/Assessments for Study BAN2401-G000-301: Randomization Phase (Visit 28 Through Visit 43 [Week 51 through 3-month Follow-up Visit]) (revised per Amendments 01, 04, 05, 06, and 08)

Phase	Randomization																	
Period	Treatment															Early Termination Visit[a]	3 Month Follow-up Visit	Un-scheduled Visit[b]
Visit[c,d]	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42		43	
Week	51	53	55	57	59	61	63	65	67	69	71	73	75	77	79			
Procedures/ Assessments																		
Vital signs[e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[f]	X	X	X
Weight	X[g]	X[h]					X[g]	X[h]							X[f]		X	X
Routine physical examination[i]		X						X							X[f]	X	X	X
12-lead ECG		X						X							X[f]	X	X	X
Urine pregnancy test[j]		X						X							X[f]	X		X
Blood for Laboratory tests[k]		X						X							X[f]	X	X	X
Urinalysis		X						X							X[f]	X		X
MMSE[l]		X						X							X[f]	X	X	X
CDR[l]		X						X							X[f]	X	X	X
ADAS-Cog14[l]		X						X							X[f]	X	X	X
EQ-5D-5L[l,m]		X													X[f]	X	X	X
QOL-AD[l,m]		X													X[f]	X	X	X
ADCS MCI-ADL[l,m]		X													X[f]	X	X	X
Zarit Burden Interview[l,m]		X													X[f]	X	X	X
C-SSRS[l]		X													X[f]	X	X	X
Safety MRI[n]		X													X[f]	X	X	X
Volumetric MRI (for PD)[o]		X													X[f]	X		X
Amyloid PET[p]		X													X[f]	X		X
Tau PET[q]				X											X[f]	X		X
Study drug administration[r]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[s]			
Blood for serum BAN2401 PK[t]		X						X						X	X[u]	X	X	X
Blood for serum anti-BAN2401 (ADA)[v]		X						X						X	X[u]	X	X	X
Blood For Exploratory PD Analysis[w]		X												X	X[f]	X		X
CSF sampling (PD, PK)[x]		X												X		X		X
Prior/concomitant meds	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[f]	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[f]	X	X	X

ADA = antidrug antibody, ADAS-Cog14 = Alzheimer's Disease Assessment Scale-Cognitive subscale14, ADCS MCI-ADL = Alzheimer's Disease Cooperative Study-Activities of Daily Living Scale for Mild Cognitive Impairment, AE = adverse event, ARIA = amyloid-related imaging abnormalities, CDR = Clinical Dementia Rating, COVID-19 = Coronavirus Disease 2019, CSF = cerebrospinal fluid, C-SSRS = Columbia-Suicide Severity Rating Scale, EQ-5D 5L = European Quality of Life–5 Dimensions 5 Level version, LP = lumbar puncture, MMSE = Mini-Mental State Examination, MRI = magnetic resonance imaging, PD = pharmacodynamic, PET = positron emission tomography, PK = pharmacokinetic, QOL-AD = Quality of Life in Alzheimer's Disease

a: Subjects who discontinue the study or study drug early must comply with the Early Termination Visit (within 7 days of the decision to early discontinue study drug) and th Follow-up Visit (3-months after the last dose of study drug). They may also have unscheduled visits for safety assessments. In addition, subjects who discontinue from stud drug are expected to return after the Early Termination Visit/Follow-up Visit for each scheduled visit when the clinical assessments of efficacy are to be conducted. At thes visits, clinical efficacy assessments (MMSE, CDR, and ADAS-Cog) will be conducted and information on concomitant medications, AEs, and SAEs will be collecte Regularly scheduled clinical efficacy visits do not need to be attended if they fall within 8 days (visit window) of the Early Termination Visit or the 3-month Follow-up Visi Subjects who discontinue from study drug are considered on study as long as they return for their regularly scheduled clinical efficacy visits as outlined above, but are nc eligible to participate in the Extension Phase. Under extenuating circumstances (eg, the COVID-19 pandemic), every effort should be made to have the Early Terminatio Visit, Follow-up Visit, and Continued Efficacy Assessment Visits conducted at the study site. However, with approval from the sponsor, subjects who cannot visit clinic sites for various reasons may have these visits performed by the home infusion staff. (revised per Amendments 01, 02, and 06)

b: Unscheduled visits may be conducted at any time that safety or safety MRI data indicate per protocol or as clinically indicated in the judgment of the investigator. Note th assessments indicated under Unscheduled Visits need not always be conducted – actual assessments needed will be determined by the investigator and will be based on th specific visit needs.

c: Assessments should take place on the first day of the study visit in the designated study week except as noted below (footnotes n, o, p, and q pertaining to imaging assessment and footnote x pertaining to CSF sample collection). A visit window of ± 8 days will be allowed for each visit; however, there must be at least 7 days between 2 infusio visits. A visit window of ± 7 days will be allowed for the Follow-up Visit (Visit 43). Visit assessments may be split over 2 consecutive days, if needed. This applies to a visits. All clinical and cognitive assessments (eg, cognitive and suicidality scales) must be completed in the prespecified order on the first day of a split visit, before collectio of ECG and other assessments. ECG and other assessments can be performed either on the first or the second day of a split visit, always before infusion. Vital signs shoul be measured, and laboratory samples should be collected on the second day, both before infusion. Note that PK samples are also required predose and following infusio (revised per Amendments 04, 06, and 08)

d: If under extenuating circumstances (eg, the COVID-19 pandemic), a subject is not able to visit the study site for scheduled safety and efficacy assessments, and th assessment(s) is/are not performed during the respective scheduled visit(s), the assessment(s) should be performed as soon as possible, either as a scheduled visit or as a unscheduled visit, unless the next scheduled assessment(s) is (are) expected to occur within 30 days. (revised per Amendment 06)

e: Vital signs will be measured both at predose and after infusion. During Visits 3, 4, 5, and 6, vital signs should be recorded at least 2 hours after study drug infusion, i addition to predose. If at those visits no untoward effects of infusion on vital signs are detected ≥2 hours after infusion, these assessments at subsequent study visits may b conducted at a shorter interval after infusion. At visits where no infusion takes place (eg, Visit 43), vital signs will be measured once. For subjects entering the Extensio Phase, vital signs at Visit 42 should be recorded at predose and at least 2 hours after study drug infusion. Vital sign measurements will consist of systolic and diastolic bloo pressure (mmHg) measured after at least 3 minutes in a semi-supine position, pulse (beats per minute), respiratory rate (per minute), and body temperature (in centigrade (revised per Amendment 01)

f: For subjects entering the Extension Phase, the indicated assessments must be performed before the 1st dose of open label treatment is administered at this visit.

g: Only subjects receiving home infusion at Visits 29 and 35 (during extenuating circumstances, eg, the COVID-19 pandemic), will have weight measurement collected Visits 28 and 34, respectively. (revised per Amendment 06)

h: Weight will be taken in the clinic at designated visits. If a subject misses a clinic visit where weight is to be collected, subsequent visits should use the most recent, previou collected weight for infusion calculations until the next clinic visit. Under such circumstances, weight is to be taken at the next clinic visit and entered into the IxRS even the visit is not designated for weight data collection. For subjects with weight measurement collected at Visits 28, and 34, weight measurement will not be needed at Visits 2 and 35. (revised per Amendment 06)

i: For subjects receiving home infusion at visits where a routine physical examination is scheduled, a symptom-directed physical examination may be performed at the discretio of the investigator if a routine physical examination is not feasible. (revised per Amendment 06)

j: Females of childbearing potential only

k: Blood for laboratory tests will be taken predose at all visits as indicated.

l: Scales are to be completed in the morning (or, if not possible, consistently at approximately the same time of day) in the following order on the days indicated: MMSE, CDR-SB, and ADAS-Cog14. For any given subject, every effort should be made to ensure that the raters for the CDR, MMSE, and ADAS-Cog14 remain unchanged throughout the study. The clinician responsible for CDR assessment must not participate in the medical management of the subjects and must be blinded to results of all safety assessments (including but not limited to results of safety MRI and clinical laboratory assessments, and AEs), except for the results of the C-SSRS. Every effort should be made to keep the site staff responsible for reviewing laboratory reports (including MRI reports) and assessing AEs separate from the site staff responsible for the MMSE and ADAS-Cog14. The EQ-5D-5L, QOL-AD, ADCS MCI-ADL, and Zarit Burden Interview will be administered after the completion of the ADAS-Cog14. Subjects and study partners (defined as a person able to support the subject for the duration of the study) need to be available in person for these assessments. However, under extenuating circumstances only, and only with the approval of the sponsor (eg, during the COVID-19 pandemic), the MMSE, CDR, ADAS-Cog14, ADCS MCI-ADL, and C-SSRS may be administered remotely via a sponsor-approved telehealth system for subjects receiving home infusion during the Randomization Phase. For subjects who are unable to travel to the study site during extenuating circumstances and home infusion is not an option, only the CDR, ADCS MCI-ADL, and C-SSRS may be administered remotely via telephone or via a sponsor-approved telehealth system. (revised per Amendments 01, 04, and 06)

m: At each visit: 3 copies of the EQ-5D-5L will be completed (Subject regarding Self [Standard Version], Partner regarding Subject [Version labeled: Proxy 1], Partner regarding Self [Standard Version], 2 copies of the QOL-AD will be completed (Subject regarding Self [Standard Version], Partner regarding Subject [Version labeled: Proxy]), 1 copy of the ADCS MCI-ADL will be completed (Partner regarding Subject), and 1 copy of the Zarit Burden Interview will be completed (Partner regarding Self [Standard Version]). All "Standard Version" questionnaires will not be labeled with those words, but they will lack a Proxy label. The subject's study partner must be available in person for these assessments. See footnote l for assessment of the ADCS MCI-ADL during the COVID-19 pandemic and other extenuating circumstances. (revised per Amendments 04 and 06)

n: MRI imaging should be conducted at any time following the completion of the immediately preceding visit and prior to each of the following Visits according the Schedule of Procedures/Assessments: Visits 7, 9, 16, 29, and 42 and at the Follow-up Visit (Visit 43). In all cases, the safety MRI must be reviewed by the imaging vendor and a local reader prior to a subject receiving the next dose of study drug. In the event of an Unscheduled Visit, the investigator in consultation with the sponsor will determine whether or not a safety MRI should be conducted. If an Early Termination Visit takes place, an MRI is to be conducted, if not already performed during the preceding 90 days. (revised per Amendment 01)

o: A volumetric MRI sequence will be collected in all subjects immediately following all safety MRI assessments. Volumetric MRI data will be analyzed at the Screening Visit (Baseline) and at 6, 12, and 18 months of treatment.

p: In the amyloid PET substudy only, amyloid PET imaging will be conducted on or within 10 days after the scheduled visits; however, subjects entering the Extension Phase must have the amyloid PET imaging performed within 10 days before study drug administration at Visit 42. Subjects who consent to participate in the amyloid PET substudy and who discontinue from the study drug will undergo an amyloid PET as part of the early termination visit only if the preceding amyloid PET assessment was performed 3 or more months before the Early Termination Visit. (revised per Amendment 06)

q: Tau PET imaging will be conducted on or within 10 days after the scheduled visit; however, subjects entering the Extension Phase must have the tau PET imaging performed within 10 days before study drug administration at Visit 42. Tau PET assessments will be performed using the sponsor-supplied tau PET imaging agent. There must be at least 48 hours between each procedure (CSF collection, amyloid PET scan, and tau PET scan). For subjects who discontinue early from the study drug, the medical monitor must be consulted before an Early Termination tau PET scan is performed. (revised per Amendments 01, 04, and 06)

r: If approved by the sponsor and allowable and conducted according to country and local guidelines, subjects may be offered the option of home infusions for all visits, except Visits 29 and 35. However, under extenuating circumstances only, and only with the approval of the sponsor (eg, during COVID-19 pandemic); home infusion at Visits 29 and 35 may be permitted. If no untoward effects of infusion are noted, during prior infusion visits, or infusion reactions can be prevented with prophylaxis, subjects will be observed 30 minutes after the end of infusion if judged medically stable by the investigator. For subjects missing 3 or more consecutive doses, and who have not had any safety assessments performed either in-clinic or at the home infusion visit(s) during the period of dose interruption, the following safety assessments must be performed before resuming study drug dosing: AE and concomitant medication assessments, vital signs, weight, routine physical (where feasible) or symptom directed physical (if routine physical is not feasible), clinical laboratory assessments, C-SSRS, and ECG. Study drug dosing may resume on the same day as these assessments (ie, before receipt of the clinical laboratory assessments results) based on the clinical judgement of the investigator. All laboratory results should be promptly evaluated by the investigator before the subsequent visit to ensure safety of continued study drug dosing. If ECG or clinical laboratory assessments cannot be conducted before restarting study drug dosing, study drug dosing may resume based on the clinical judgement of the investigator. However, these assessments must be performed as soon as possible and results should be promptly evaluated by the investigator before subsequent visits to ensure safety of continued study drug dosing. (revised per Amendments 05 and 06)

s: Study drug administration will occur only for subjects entering the Extension Phase. At this visit, th[s] 1st dose of open label BAN2401 will be administered after the completion of all end of study safety and efficacy assessments (denoted by footnote f). Subjects must stay in clinic for 4 full hours following administration for safety observation during thi[s] 1st infusion visit. No home infusion is permitted at this visit. (revised per Amendments 04, 06, and 08)

t: At Visits 29, 35, and 41, blood will be taken for the BAN2401 assay both predose and at least 2 hours after the end of infusion. If study drug is administered at the study site, subjects are required to remain in clinic for safety observation for at least 2 hours following infusion at visits where PK samples are taken. If study drug is administered at a location other than the study site (eg, subject's home), the infusion staff may collect the PK samples any time after 2 hours (revised per Amendments 01 and 06)

u: Only for subjects entering the Extension Phase, blood will be collected at predose for PK and anti-BAN2401 antibody (ADA) analyses and 2 hours postdose for PK analysis. No blood samples for PK and ADA analyses will be collected at this visit for subjects not entering the Extension Phase. (revised per Amendment 06)

v: Blood for the BAN2401 antidrug antibody assay will be taken predose at all indicated visits.

w: Blood for plasma isolation for exploratory biomarker assessments will be collected for all subjects. At Visit 42, subjects entering the Extension Phase must have blood for plasma isolation collected at predose. For subjects not entering the Extension Phase, blood will be collected at any time during the visit. (revised per Amendments 04 and 06)

x: Subjects on anticoagulant therapy are not permitted to participate in CSF sampling. Those subjects who consent to CSF assessments should have CSF drawn via LP 2-4 days after Visit 29 (12 months infusion) and Visit 41, and serum PK samples should be taken immediately following the CSF collection. Subjects who discontinue early from the study drug will have CSF drawn if only if the early termination visit occurs on or after Week 39 and the preceding CSF assessment was performed 3 or more months before the Early Termination Visit. (revised per Amendments 01, 04, and 05)

12.1.2. Sponsor's Grading for Laboratory Values

Table 36 Sponsor's Grading for Laboratory Values

	Grade 1	Grade 2	Grade 3	Grade 4
BLOOD/BONE MARROW				
Hemoglobin	<LLN – 10.0 g/dL <LLN – 100 g/L <LLN – 6.2 mmol/L	<10.0 – 8.0 g/dL <100 – 80 g/L <6.2 – 4.9 mmol/L	<8.0 g/dL <80 g/L <4.9 mmol/L; transfusion indicated	life-threatening consequences; urgent intervention indicated
Leukocytes (total WBC)	<LLN – 3.0×10^9/L <LLN – 3000/mm^3	<3.0 – 2.0×10^9/L <3000 – 2000/mm^3	<2.0 – 1.0×10^9/L <2000 – 1000/mm^3	<1.0×10^9/L <1000/mm^3
Lymphocytes	<LLN – 800/mm^3 <LLN – 0.8×10^9/L	<800 – 500/mm^3 <0.8 – 0.5×10^9/L	<500 – 200/mm^3 <0.5 – 0.2×10^9/L	<200/mm^3 <0.2×10^9/L
Neutrophils	<LLN – 1.5×10^9/L <LLN – 1500/mm^3	<1.5 – 1.0×10^9/L <1500 – 1000/mm^3	<1.0 – 0.5×10^9/L <1000 – 500/mm^3	<0.5×10^9/L <500/mm^3
Platelets	<LLN – 75.0×10^9/L <LLN – 75,000/mm^3	<75.0 – 50.0×10^9/L <75,000 – 50,000/mm^3	<50.0 – 25.0×10^9/L <50,000 – 25,000/mm^3	<25.0×10^9/L <25,000/mm^3
METABOLIC/LABORATORY				
Albumin, serum-low (hypoalbuminemia)	<LLN – 3 g/dL <LLN – 30 g/L	<3 – 2 g/dL <30 – 20 g/L	<2 g/dL <20 g/L	life-threatening consequences; urgent intervention indicated
Alkaline phosphatase	>ULN – 3.0×ULN	>3.0 – 5.0×ULN	>5.0 – 20.0×ULN	>20.0×ULN
ALT	>ULN – 3.0×ULN	>3.0 – 5.0×ULN	>5.0 – 20.0×ULN	>20.0×ULN

AST	>ULN – 3.0×ULN	>3.0 – 5.0×ULN	>5.0 – 20.0×ULN	>20.0×ULN
Bilirubin (hyperbilirubinemia)	>ULN – 1.5×ULN	>1.5 – 3.0×ULN	>3.0 – 10.0×ULN	>10.0×ULN
Calcium, serum-low (hypocalcemia)	<LLN – 8.0 mg/dL <LLN – 2.0 mmol/L	<8.0 – 7.0 mg/dL <2.0 – 1.75 mmol/L	<7.0 – 6.0 mg/dL <1.75 – 1.5 mmol/L	<6.0 mg/dL <1.5 mmol/L
Calcium, serum-high (hypercalcemia)	>ULN – 11.5 mg/dL >ULN – 2.9 mmol/L	>11.5 – 12.5 mg/dL >2.9 – 3.1 mmol/L	>12.5 – 13.5 mg/dL >3.1 – 3.4 mmol/L	>13.5 mg/dL >3.4 mmol/L
Cholesterol, serum-high (hypercholesterolemia)	>ULN – 300 mg/dL >ULN – 7.75 mmol/L	>300 – 400 mg/dL >7.75 – 10.34 mmol/L	>400 – 500 mg/dL >10.34 – 12.92 mmol/L	>500 mg/dL >12.92 mmol/L
Creatinine	>ULN – 1.5×ULN	>1.5 – 3.0×ULN	>3.0 – 6.0×ULN	>6.0×ULN
GGT (γ-glutamyl transpeptidase)	>ULN – 3.0×ULN	>3.0 – 5.0×ULN	>5.0 – 20.0×ULN	>20.0×ULN
Glucose, serum-high (hyperglycemia)	Fasting glucose value: >ULN – 160 mg/dL >ULN – 8.9 mmol/L	Fasting glucose value: >160 – 250 mg/dL >8.9 – 13.9 mmol/L	>250 – 500 mg/dL; >13.9 – 27.8 mmol/L; hospitalization indicated	>500 mg/dL; >27.8 mmol/L; life-threatening consequences
Glucose, serum-low (hypoglycemia)	<LLN – 55 mg/dL <LLN – 3.0 mmol/L	<55 – 40 mg/dL <3.0 – 2.2 mmol/L	<40 – 30 mg/dL <2.2 – 1.7 mmol/L	<30 mg/dL <1.7 mmol/L life-threatening consequences; seizures
Phosphate, serum-low (hypophosphatemia)	<LLN – 2.5 mg/dL <LLN – 0.8 mmol/L	<2.5 – 2.0 mg/dL <0.8 – 0.6 mmol/L	<2.0 – 1.0 mg/dL <0.6 – 0.3 mmol/L	<1.0 mg/dL <0.3 mmol/L life-threatening consequences
Potassium, serum-high (hyperkalemia)	>ULN – 5.5 mmol/L	>5.5 – 6.0 mmol/L	>6.0 – 7.0 mmol/L hospitalization indicated	>7.0 mmol/L life-threatening consequences
Potassium, serum-low (hypokalemia)	<LLN – 3.0 mmol/L	<LLN – 3.0 mmol/L; symptomatic; intervention indicated	<3.0 – 2.5 mmol/L hospitalization indicated	<2.5 mmol/L life-threatening consequences
Sodium, serum-high (hypernatremia)	>ULN – 150 mmol/L	>150 – 155 mmol/L	>155 – 160 mmol/L hospitalization indicated	>160 mmol/L life-threatening consequences
Sodium, serum-low (hyponatremia)	<LLN – 130 mmol/L	N/A	<130 – 120 mmol/L	<120 mmol/L life-threatening consequences
Triglyceride, serum-high (hypertriglyceridemia)	150 – 300 mg/dL 1.71 – 3.42 mmol/L	>300 – 500 mg/dL >3.42 – 5.7 mmol/L	>500 – 1000 mg/dL >5.7 – 11.4 mmol/L	>1000 mg/dL >11.4 mmol/L life-threatening consequences
Uric acid, serum-high (hyperuricemia)	>ULN – 10 mg/dL (≤0.59 mmol/L) without physiologic consequences	N/A	>ULN – 10 mg/dL (≤0.59 mmol/L) with physiologic consequences	>10 mg/dL >0.59 mmol/L life-threatening consequences

Source: Protocol BAN2401-G000-301 version 12.0/24 Aug 2022 (per Amendment 10), table 4 ALT = alanine aminotransferase (serum glutamic pyruvic transaminase), AST = aspartate aminotransferase (serum glutamic oxaloacetic transaminase), N/A = not applicable, LLN = lower limit of normal, ULN = upper limit of normal, WBC = white blood cell.
Based on Common Terminology Criteria for Adverse events (CTCAE) Version 4.0. Published: May 28, 2009 (v4.03: June 14, 2010).

12.1.3. Death Narratives for 301 Core and OLE

Study 301 Core narratives of subjects receiving lecanemab who died during the study

(b) (6)

This is an 85-year-old female with past medical history of mild AD, tremor, balance disorder and mixed deafness, who has been on anti-inflammatory and antirheumatic agents, non-steroids (Megared 4 in 1 supplement daily) and antirheumatic medications, who received the last dose (28th dose) of study drug on day 421. On study day 434, the subject died. The cause of death was unknown, and no autopsy was performed.

Reviewer Comment: In this subject's case the cause of death is unknown and therefore, the relatedness to study drug is difficult to determine. The narrative is silent to cardiovascular or pulmonary disease, or other conditions that may increase risk of sudden death. There is no description of the circumstances leading to death included in the narrative.

(b) (6)

This 79-year-old male, with an ApoE ε3/ε3 genotype, had a relevant past medical history of chronic kidney disease, impaired fasting glucose, coronary artery disease (s/p stenting and CABG), chronic obstructive pulmonary disease (COPD), hypertension, hyperlipidemia. He was on a baby aspirin. On study day 56, he was diagnosed with atrial fibrillation and started on apixaban 5 mg po daily. He received the 18th dose of the study drug on study day 237. On study day 263 he experienced left sided weakness. A perfusion CT showed a large perfusion defect in the right middle cerebral artery territory with large area of penumbra and reduced cerebral blood flow. A large filling defect consistent with a thrombus at the terminal portion of the right ICA proximal M1 segment of right MCA and proximal aspect of the A1 segment of the right ACA was noted. Unspecified treatment was reported. He was admitted to the hospital. His laboratory tests showed elevated B-type natriuretic peptide, and low albumin and calcium, sodium, and total protein levels. Troponin was elevated as well. On an unknown date he had a G-tube places due to difficulty with swallowing and risk of aspiration. Following G-tube placement patient became septic and sepsis protocol initiated with patient being placed on ventilator. His condition declined rapidly and on study day 282 he was removed with the respirator and died.

Reviewer Comment: This subject had multiple risk factors for stroke, and stroke and related death due to complications of hospitalization and interventions resulting from stroke, are not related to study drug.

(b) (6)

This 70 year-old-male, with an ApoE ε3/ ε3 genotype, had a relevant past medical history of hyperlipidemia, hypertension, type II DM, and coronary artery disease. The subject received the 17th dose (last dose) of study drug on study day 220. On study day 230, subject experienced shortness of breath and died suddenly. The event was reported as a suspected myocardial infarction. Autopsy was not performed, and the cause of death was unknown.

Reviewer Comment: While the exact cause of death in this subject was not known, the subject had significant cardiovascular risk factors and cardiac disease and I could not identify a clear role of study drug.

(b) (6)

88-year-old female, with an ApoE ε 3/ ε3 genotype, with relevant past medical history of aortic arteriosclerosis, coronary artery disease, diabetes (and diabetic neuropathy and nephropathy), hypertensive heart disease, hypertension, hyperlipidemia, pulmonary hypertension, AV block, COPD who received the 25th dose (last dose) of study drug on study day 330. On study day 347 the subject experienced atrial fibrillation with rapid ventricular response and pulmonary edema and was hospitalized. On study day 351 the subject underwent an esophagogastroduodenoscopy with ablation of an arteriovenous malformation. On the same day the subject experienced a cardiac arrest which resolved with sequala with onset of respiratory failure and pneumonia and prolonged hospitalization. On study day 351, the subject was intubated and treated with antibiotics, and on study day 364 she underwent a tracheostomy and PEG placement. On study day 376, she was weaned from assist-control mode and a CT revealed a pulmonary embolism leading to further prolonged hospitalization. Due to the history of AVM, she could not be started on anticoagulation. She was discharged to a long-term care facility on Study day 390. On study day 405 the subject died, presumed to be due to respiratory failure but no records were available from the care facility.

Reviewer Comment: In this case death seems to be related to patient's underlying cardiovascular disease, and arteriovenous malformation, and complications of prolonged hospitalization due to this. I could not identify a role of study drug in this death.

(b) (6)

This 79-year-old white female, with an ApoE ε3/ ε4 genotype, had a relevant past medical history of Type 2 diabetes mellitus angina pectoris, hypertension. She had been on metformin, apixaban, metoprolol and insulin. She received the 36th dose (last dose) of study drug on study day 491. On study day 526 she presented to the emergency room with acute mental status changes and was diagnosed with diabetic ketoacidosis. Her lactate level was above 6. She was also found to have a UTI and started on antibiotics. On the same day the patient died with the cause of death reported to be diabetic ketoacidosis.

Reviewer Comment: The death in this case was likely due to patient's underlying diabetes. I could not identify a role of study drug in this case.

(b) (6)

77-year-old male with an ApoE ε3/ ε4 genotype and past medical history of onychomycosis, hordeolum, MCI, anxiety, bradycardia, hyperlipidemia, constipation, insomnia, coronary artery disease, hepatitis, scarlet fever and tonsillectomy. He received the 38th (last dose) of study drug on study day 519. On study day 526 behavior changes with increased disorientation, decreased oral fluid intake and difficulty walking and moving was noted. On study day 534 the patient was taken to the ER where work up revealed increased white blood cell count and reduced platelet count, and chest x-ray was suggestive of possible pneumonia. The subject received iv antibiotics. On study day 535 an MRI showed ventriculomegaly and abdominal ultrasound showed liver heterogeneity and pleural effusion. A lumbar puncture showed RBC of 600 and WBC of 17, which were thought to be due to CSF contamination with blood. Repeat WC count was elevated in the range of 20,000/ML. Flow cytometry of both blood and CSF was suggestive of abnormal population of T-cell lymphocytes and T cell receptor rearrangement. On study day 538, further evaluation showed pleural effusion. On study day 552, repeat LP showed RBC of 0 and WBC of 40 suggesting pleocytosis. Flow cytometry was consistent with t-cell lymphoma. On Study day 561 the subject as discharged from the hospital and placed on lorazepam and morphine for comfort, and on study day 563 died of lymphomatous meningitis.

Reviewer Comment: Given the relatively short duration of exposure, and the latency usually seen in cancer onset after an exposure, and the higher prevalence of lymphoma in older age, I cannot identify a clear role in this patient's death due to metastatic lymphoma.

(b) (6)

76-year-old male with an ApoE ε3/ε3 genotype relevant past medical history of DM and coronary artery disease received the 20th dose (last dose) of study drug on study day 366. On study day 375, the subject experienced generalized weakness and fever. The fever persisted for 2 days and improved on study day 377. On study day 382 the subject experienced dyspnea with fever. On study day 383 COVID testing was positive and the subject was hospitalized and on study day 395 was admitted to the ICU. On study day 402 the subject died due to cardiorespiratory arrest.

Reviewer Comment: Cause of death in this subject was COVID-19 related pneumonia and was not related to study drug.

301 OLE narratives of subjects receiving lecanemab who died during the 301 OLE phase

(b) (6)

78-year-old female who received placebo during 301 Core with an ApoE ε3/ ε4 genotype and relevant past medical history of carotid artery stenosis, mild cognitive impairment due to

Alzheimer's disease, glaucoma, hypertension, hyperlipidemia, cardiac murmur, carotid bruit, sleep apnea. Her concomitant medications included naproxen, oxycodone, paracetamol, hydrochlorothiazide, metoprolol, nitrofurantoin, rosuvastatin, tramadol, levothyroxine and baby aspirin. She received the first dose of extension study on extension day 1. On extension day 11, she experienced a myocardial infarction which resulted in death.

Reviewer Comment: This subject's death occurred within 10 days after her first exposure to study drug as she was on placebo before. While I cannot rule out a role of study drug due to the proximity of the death to the first dose of study drug, she had significant risk factors which likely caused the myocardial infarction.

(b) (6)

68-year-old male who was randomized to placebo during 301 Core, received the first dose of study drug on extension day 1. He had an ApoE ε3/ε3 genotype and relevant past medical history included Type 2 DM, MCI due to AD, hypertension. On extension day 103, the subject had cough, cold symptoms and fever. He was diagnosed with COVID-19 pneumonia on the same day. On extension day 108, his symptoms worsened with flu-like illness, increased weakness, confusion from baseline and headache. He was hospitalized. Chest x-ray showed bilateral infiltrate indicating pneumonia. On an unknown date subject was discharged to hospice care and died on extension day 129.

Reviewer Comment: This subject died due to COVID19 and the study drug did not appear to play a role in this subject's death.

(b) (6)

81-year-old male was received LEC10BW during his participation in 301 Core, with an ApoE ε3/ ε3 genotype, who had no documented medical history that includes cardiac risk factors. On extension day 134 the subject received the 11th dose of study drug. On extension day 153, the subject experienced acute cardiac failure resulting in death. The subject was found lying in bathtub of an open-air bath and was immediately transported to another hospital where he was declared dead. No autopsy was performed.

Reviewer Comment: While this subject's narrative is silent to cardiac risk factors, the subject's cardiac arrest occurred 19 days after the 11th dose of study drug. Due to lack of more information, no clear conclusions can be made on the role of the study drug in this death.

(b) (6)

64-year-old female, with a ApoE ε2/ ε4 genotype, received placebo during the 301 Core. She received the 13th dose of study drug on extension day 173. In extension day 188, she was in a road traffic accident, which was fatal. Autopsy was not performed.

(b) (6)

85-year-old male, with a ApoE ε3/ ε4 genotype, received placebo during the 301 Core. Study. His relevant past medical history includes atrial fibrillation, hypertension, dyslipidemia, cardiac valve disease, hyperglycemia. He received the 37th dose of study drug on extension day 505. On extension day 515, he presented to the ER with COVID-19 and was discharged the same day. On extension day 516, he fell and had increased weakness and difficulty ambulating. He was transferred to the hospital via ambulance, and started on azithromycin, ceftriaxone and dexamethasone, famotidine and guaifenesin and nebulizer, and oxygen. On extension day 519 he died in the hospital due to COVID-19. No autopsy was performed.

Reviewer Comment: In both of the cases described above, I could not identify a role of study drug in the subjects' death.

(b) (6)

This is an 80-year-old female, with an ApoE ε3/ε4 genotype, who was randomized to receive lecanemab during the 301 Core study. Her past medical history includes a lacunar infarct, mild AD, history of presyncope, hypertonic bladder, hyperlipidemia, and hypertension. She received the 34th dose of study drug and on Study day 488 she was diagnosed with pancreatic cancer, with anorexia, SBP of 100mmHG and weight loss, and abdominal pain. Patient chose a non-aggressive treatment plan and home end-of life care was requested. Study drug was discontinued, and she passed away on Study day 496.

Reviewer Comment: This death, which occurred 5 days after the 90-Day data cut off of December 1, 2022, was included in the AE dataset. In this patient's case, I cannot identify a clear role of study drug in the diagnosis of pancreatic cancer, her risk factors included age.

12.1.4. SAE and Other Narratives and Tables for Study 301 Core and 301 OLE

I reviewed the narratives of SAEs related to events of special interest across the clinical program (ARIA-E, ARIA-H, cerebral hemorrhage and infusion related reactions, immunogenicity, hypersensitivity, seizures), SAEs occurring in at least 2 or more subjects receiving lecanemab compared to placebo in the 301 Core study, and narratives of potentially medically significant events (injuries and accidents, syncope, seizures, , pulmonary embolism) and designated medical events in lecanemab treated subjects during the Study 301(Core and OLE), and the 201 OLE study. Additionally, I reviewed SAEs occurring in 3 or more subjects during the 301 OLE. For 201 OLE, previously reviewed narratives at the time of the original submission will not be included in this review.

For narratives the following SAEs of designated medical events or medical events of interest were also included: acute respiratory failure/respiratory failure (b) (6), rhabdomyolysis (b) (6)), motor neuron disease (b) (6)), death (sudden death) (b) (6)), acute kidney injury, ((b) (6)), seizure not

associated with ARIA ([redacted]), and seizures related to ARIA or cerebral hemorrhage ARIA [redacted]) in the Core. In the 301 OLE as of data cutoff of December 1, 2022, 13 subjects had a seizure while on lecanemab. Of these, 6/13 ([redacted]) occurred in the setting of ARIA, and one in the setting of cerebral hemorrhage ([redacted] Six subjects (6/1315, 0.4%) had a seizure [redacted] which was not associated with ARIA-E or ARIA-H. Additionally the following SAEs were reviewed: suicide attempt ([redacted]), and SAEs of fractures.

Blinded narratives from study 303 will only be briefly described if related to an SAE of special interest (ARIA-E, ARIA-H, infusion related reaction or other hypersensitivity, immunogenicity).

Subdural Hemorrhage/Subdural Hematoma

Four subjects [redacted],) on lecanemab in 301 Core and two subjects [redacted] in 301 OLE had an SAE of subdual hemorrhage. Subject [redacted] who had a subdural hemorrhage which was not serious will be briefly described as well. I reviewed these narratives. Subject [redacted] who is an 81-year-old was diagnosed with chronic subdural hematoma on Study day 359, 4 days after the last dose of study drug. Subject [redacted] who was a 90-year-old male had sustained a fall about a month prior to first dose of study drug, experienced progressive worsening gait and found to have bilateral chronic subdural. None of these subjects experienced ARIA. Given that advanced age, and trauma is a risk factor for subdural hematoma /hemorrhage, I could not identify a role of study drug in these SAEs of subdural hematoma. Subject [redacted] had a subdural hematoma in the setting of a self-inflicted injury with a bullet grazing his head. Subject [redacted], sustained a fall and found to have subarachnoid hemorrhage and subsequently a subdural hematoma that was not an SAE. Subject [redacted] a 68-year-old who sustained subdural hematomas subsequent to a fall. Subject [redacted], a 56-year-old ApoE heterozygote, who received placebo during the Core study, and was not on an antithrombotic. On extension day 167, on the day of the 13th dose of lecanemab, he sustained a subdural hematoma, which was moderate and nonserious, but enlarged resulting in midline shift on day 190. He was hospitalized and also complained of mild intermittent headaches. He underwent a PVA embolization of the frontal and parietal branches of the left middle meningeal artery, but post procedure imaging showed expansion of the hematoma which then was evacuated via a craniotomy. No clear etiology was identified, and there was no accompanying ARIA. Study drug was temporarily interrupted and restarted. He had the 16th dose on extension day 280 and his participation in the extension OLE is ongoing as of the data cut off of December 1, 2022. I could not identify a clear role of study drug in these incidents.

Narratives of SAEs occurring in ≥ 2 subjects on LEC10-BW compared to placebo in 301 Core

Atrial Fibrillation

There were 7 subjects ([redacted]), who experienced an SAE of atrial fibrillation while receiving lecanemab in 301 Core and two subject

(b) (6)) who had an SAE of atrial fibrillation in the OLE. All of the subjects had advanced age and hypertension as risk factors for atrial fibrillation. Additionally, subjects (b) (6) had pre-existing cardiac disease, with subjects (b) (6), (b) (6) having pre-existing atrial fibrillation. The time of diagnosis of atrial fibrillation in relation to the infusion ranged from 0-17 days.

In three subjects diagnosis of atrial fibrillation or symptoms of atrial fibrillation occurred within 0-3 days of the infusion and will be described further. Subject (b) (6) experienced a serious infusion related reaction starting 2.5 hours after the first dose of study drug in 301 Core, with nausea vomiting, fever, chills, elevated blood pressure and heart rate. ECG showed sinus tachycardia. Her symptoms resolved 3 days later; at which time she was also noted to be in atrial fibrillation. Subject (b) (6) reported feeling shaky with chest tightness after the 8th infusion on study day 98. She also reported feeling this way on and off for the past two months. In the hospital she was diagnosed with angina pectoris with exertional dyspnea with ECG showing a left bundle branch block and frequent supraventricular tachycardia. She received the 10th dose of study drug on study day 132. On study day 141 she presented to the ER with palpitations and chest discomfort and diagnosed with atrial fibrillation. She was started on apixaban and completed study 301 Core with no complications. Subject (b) (6) received the 19th dose of study drug on study day 267, and on the same day, ECG showed atrial fibrillation. He was started on baby ASA and apixaban and completed study as planned.

Reviewer Comment: In subject (b) (6) it is difficult to rule out a role for the infusion related reaction in response to lecanemab in triggering atrial fibrillation". It is possible that, similar to other medical conditions (e.g., infections, hypoxemia), the physical stress of the infusion related reaction may have triggered onset of atrial fibrillation in this subject who had underlying risk factors. In subject (b) (6) the onset of palpitations, shakiness and chest tightness ongoing for months appear to align with study participation, with symptoms also occurring after an infusion one time after the 8th infusion. I cannot rule out that study drug administration triggered atrial fibrillation in this patient with other underlying risk factors for atrial fibrillation. In the case of (b) (6), atrial fibrillation was discovered after the 19th dose of study drug, as part of a study ECG in an asymptomatic patient. It is possible that in this case, atrial fibrillation may have been ongoing prior to the infusion, and discovered due to scheduled ECG at that time. Thus, I cannot identify a clear role of study drug in this case, given his other underlying risk factors.

<u>Angina pectoris/acute myocardial infarction/myocardial infarction/coronary artery disease/coronary artery stenosis</u>

Three subjects (b) (6)) in 301 Core, and 3 subjects in 301 OLE (b) (6)) had an SAE with PT of myocardial infarction or acute myocardial infarction. 6 subjects (b) (6)

(b) (6)) in 301 Core, and none in 301 OLE had an SAE of angina pectoris. Two subjects (b) (6)) in 301 Core had an SAE of coronary artery disease and one subject (b) (6)) in 301 OLE had an SAE of coronary artery stenosis.

All of these subjects had one or more risk factor for coronary artery disease (such as hypertension, hyperlipidemia, diabetes), and 6 subjects (b) (6)) had a history of cardiac disease in addition to other risk factors. I could not identify a clear role of study drug in these SAEs. In one subject ((b) (6) the presumed myocardial infarction resulted in sudden death; the narrative of this subject is described under Section 12.1.3. In two subjects (b) (6) and (b) (6), angina occurred after the infusion.

Reviewer Comment: While I cannot rule out a role of study drug in (b) (6) and (b) (6) both of these subjects experienced similar chest pain, outside of the infusions and have cardiovascular risk factors, making it difficult to ascertain relatedness to study drug.

Syncope
There were 6 subjects (b) (6)) receiving LEC-10BW in 301 Core who had one or more episode of syncope. Two subjects had an SAE of syncope in 301 OLE ((b) (6)).

Reviewer Comment: I reviewed these narratives and could not identify a clear role of study drug. All subjects had other risk factors or events likely to trigger the syncope including, cardiovascular risk factors, cardiac disease, medications, or medical conditions (such as acute cholangitis) that likely triggered the syncope.

Non-cardiac chest pain
Four subjects ((b) (6)) receiving LEC-10BW, all in 301 Core, experienced noncardiac chest pain. There was one SAE of non-cardiac chest pain in the 301 OLE study ((b) (6)). I could not identify a clear role of study drug in these events. In three subjects it was felt that gastroesophageal reflux may have played a role (b) (6). In one subject, (b) (6) troponin was mildly elevated during brief hospitalization, and she was started on metoprolol. In one subject ((b) (6)), brief episodes of chest pain occurred during study drug infusion, and he was sent to the ER with a negative cardiac work up, and wife mentioning this is similar to his GERD related pain. In all of these cases occurring during the Core, the subjects continued with study participation without any further events and entered 301 OLE. Subject (b) (6) received placebo during the Core. He received the 5th dose of study drug on extension day 57, and on extension day 68 found to have radiographically moderate ARIA-E and ARIA-H (wit 42 microhemorrhages). On extension day 75 he experienced non-cardiac chest pain and elevated blood pressure (152/82 mmHg), and work up revealed no clear etiology, with normal echocardiogram, EKG, and CT of the chest. The noncardiac chest pain resolved the next day.

Reviewer Comment: I could not identify a clear role of study drug in any of these events.

Diverticulitis

There were 4 subjects [redacted] who had an SAE of diverticulitis while receiving LEC10-BWin 301 Core Study, and none in 301 OLE. One subject [redacted]) had pre-existing diverticulitis, subject [redacted] had co-occurring COVID-19 infection at the time of onset of diverticulitis. In the other subjects I could not identify clear risk factors for diverticulitis. In three cases [redacted]) no action was taken with study drug, and diverticulitis was treated, and the subjects continued with study participation and completed 301 Core and entered 301 OLE without any further events. Subject [redacted] presented with fever and possible seizures, on study day 213, and noted to be febrile in the hospital with work up revealing diverticulitis and leukopenia. She was also diagnosed with COVID-19. She was treated with antibiotics and levetiracetam. Study drug was temporarily interrupted and then resumed. She received the last dose of study drug on study day 421, and withdrew from study on study day 435.

Reviewer Comment: I reviewed these narratives and could not identify a clear role of study drug r as study drug was continued in all of these cases without recurrence of diverticulitis.

Fall

There were 3 subjects [redacted]) who had an SAE of fall during 301 Core and two [redacted]) during 301 OLE. Subject [redacted] had risk factors for fall (history of falls and balance disorder, neurosensory deafness, spinal stenosis, osteoarthritis), subject [redacted] had a mechanical fall while climbing a ladder, and subject [redacted] appeared to have a fall in the context of alcohol intoxication. Subject [redacted] had a fall in the shower and found by husband with no recollection of the fall, three days after an infusion related reaction, and ongoing flu like symptoms she was also found to have RSV and mild renal impairment and treated with doxycycline and iv fluids in the hospital with resolution of symptoms. I cannot rule out a role of study drug related infusion reaction in her fall, although the presence of an RSV infection, likely contributed as well. Subject [redacted] completed Core on lecanemab, and on extension day 133 sustained a fall, with no memory of the incident. Work up in the hospital did not identify any clear etiology, MRI brain showed increased signal on DWI with no corresponding flair and was thought to be artifactual. After discharge from the hospital, he resumed participation in the Core study and received 11th dose of study drug on extension day 155 and his participation in the OLE is ongoing as of data cut off of December 1, 2022.

Reviewer Comment: I reviewed these narratives, and could not identify a clear role of study drug in these falls.

Acute Kidney injury:

There were two subjects (b) (6)) in 301 Core who had an SAE of acute kidney injury and one subject (b) (6) in the 301 OLE. In the case of subject (b) (6) acute kidney injury occurred in the setting of an acute infection of pneumonia, dehydration, urinary retention and was unlikely to be related to study drug. In the case of subject (b) (6), who had a relevant past medical history of arterial occlusive disease, hypertension and dyslipidemia, and relevant medications of allopurinol, the subject started experiencing elevation in creatinine starting on study day 442 and work up with biopsy revealed acute tubulointerstitial nephritis on a background of moderate chronic tubulointerstitial nephritis with active interstitial lesions and tubulitis. The infiltrate was polymorphic lymphoplasmacytic with a predominance of plasmacyte. An IGG4 labeling study, used to support a diagnosis of interstitial nephritis and other inflammatory conditions, was borderline positive. Subject (b) (6) with relevant past medical history of hepatic steatosis, arteriosclerosis, cough, received the 10th dose of study drug on extension day 137, and on extension day 147 experienced a respiratory tract infection. On extension day 151, she received the 11th dose of study drug, and presented to the emergency room with shortness of breath and cough. She was diagnosed with bibasilar atypical pneumonia, cardiomegaly and hypoxia and was hospitalized. X-ray showed diffuse interstitial thickening and cardiac enlargement likely CHF. She was treated with ceftriaxone and azithromycin, steroids and inhalers and analgesics and narcotics. Her CT chest showed multiple ground glass opacities in the bilateral lungs, consistent with interstitial lung disease. It also showed bilateral bronchial wall thickening was seen with acute and or chronic bronchitis, and multiple bilateral subcentimer pulmonary nodules, likely post infectious in etiology. The central pulmonary arteries were dilated as seen in the setting of pulmonary hypertension. Symptoms of atypical, bibasilar pneumonia and hypoxia resolved on extension day 158 she was discharged from the hospital. She received the 12th dose of study drug on extension day 167. On extension day 176 she presented to the ER with shortness of breath and nonserious skin rash. She was hospitalized for acute respiratory failure, eosinophilic pneumonia, interstitial lung disease, pulmonary pass, mediastinal lymphadenopathy, hilar lymphadenopathy, abnormal weight loss, rheumatoid arthritis and acute kidney injury. She was treated with vancomycin, methylprednisolone, ceftriaxone, inhalers, iv fluid, cefuroxime, escitalopram, nebulizers, furosemide, heparin, analgesics, zolpidem, and pantoprazole. She remained in the hospital with permanent oxygen use. Respiratory failure resolved on study day 184. Acute kidney injury, eosinophilic pneumonia, abnormal weight loss resolved on study day 196. Her symptoms resolved on study day 196. As of data cut off of December 01, 2022, her participation was ongoing.

Reviewer Comment: I cannot identify a clear role of study drug in subject (b) (6)s acute kidney injury which occurred in the setting of pneumonia and urinary retention, and resolved with supportive treatment during hospital stay. I cannot rule out a role of study drug in the case of subject (b) (6) Since acute interstitial nephritis can be caused by drugs, I can't rule out a role of study drug in this case; however, it is also possible that it may be related to allopurinol which the patient has been on and is known to cause tubular interstitial nephritis. The subject completed 301 Core and enrolled in 301 OLE. In the case of subject (b) (6) it is possible that

acute illness, and medications (ceftriaxone and azithromycin may have contributed to acute kidney injury.

Cellulitis

There were two subjects ((b) (6) who had an SAE of cellulitis in 301 Core (none in OLE). Subject (b) (6) sustained a wound in his right knee while using a tool at work which started out as a cellulitis and turned into osteomyelitis. The subject had underlying diabetes mellitus as risk factor. The other subject had cellulitis of the right great toe, with underlying risk factors of neuropathy, hammer toes, history of bilateral toe amputations due to neuropathy, peripheral venous disease, and past occurrence of cellulitis.

Reviewer Comment: I reviewed these narratives and did not identify a clear role of study drug.

COVID-19 pneumonia

There were 4 subjects who had an SAE of COVID-19 pneumonia, 2 ((b) (6)) in 301 Core, and 2 in 301 OLE (b) (6)).

Reviewer Comment: I reviewed the narratives of these subjects, as well as those who had an SAE of COVID-19, death due to COVID-19, and could not identify a clear role of study drug.

Diarrhea

Two subjects ((b) (6)) receiving LEC10-BW in 301 Core experienced an SAE of diarrhea. In the case of (b) (6) , it is possible that the diarrhea, nausea, vomiting was due to gastroenteritis, as this resolved with supportive treatment during hospitalization, did not recur, and subject completed 301 Core and entered OLE. In the case of (b) (6) intermittent diarrhea, fatigue and weight loss started during treatment with lecanemab on study day 450, and led to subject withdrawing from study, with no clear etiology identified.

Reviewer Comment: I could not identify a clear role of study drug in subject (b) (6) , but cannot rule out a role of study drug, in subject (b) (6) diarrhea, fatigue and weight loss, as no clear alternative etiology was identified. This said, this subject's past medical history did included some risk factors for gastrointestinal disease including a history of colectomy and intestinal diverticulum in (b) (6) and cholelithiasis and cholecystectomy which may have contributed to symptoms.

Hyponatremia

Three subjects receiving lEC10-BW experienced an SAE of hyponatremia, 2 ((b) (6) (b) (6)) during 301 Core and two (b) (6)) during 301 OLE. In the case of (b) (6) , hyponatremia occurred in the setting of small cell lung cancer. Subject (b) (6) had excessive free water intake without any other oral intake, and in subject (b) (6) , it occurred in the context of nausea, vomiting and lack of po intake in the setting of severe constipation, and for subject. In subject (b) (6) , while there was no clear cause, patient did have a history of hyponatremia, and was on lisinopril which may have worsened hyponatremia.

Reviewer Comment: I reviewed these narratives and could not identify a clear role of study drug in these instances.

Invasive/infiltrating ductal breast carcinoma

Two subjects ([(b) (6)] were diagnosed with invasive or infiltrative ductal breast cancer during their participation in 301 Core. Subject [(b) (6)] was diagnosed with Grade 3 infiltrating ductal carcinoma on study day 238, and subject [(b) (6)] was diagnosed with invasive ductal breast cancer on study day 299. Both received treatment for the cancer, and completed 301 Core and entered OLE.

Reviewer Comment: Given the long exposure and latency usually seen for cancers, I cannot identify a clear role of study drug in these instances.

Pulmonary edema/Acute pulmonary edema

Two subjects [(b) (6)]) receiving lecanemab had an SAE of pulmonary edema, and one subject [(b) (6)] of acute pulmonary edema while participating in the 301 Core study (none in 301 OLE). , Both subjects [(b) (6)] had underlying cardiac disease as risk factors. Subject [(b) (6)] had acute pulmonary edema, in the setting of prolonged hospitalization due to severe symptomatic ARIA-E. See Section 12.1.4 for these narratives. Subject [(b) (6)]'s narrative will be described under Section 12.1.9.

Reviewer Comment: I could not identify a clear role of study drug in the SAEs of pulmonary edema in two participants with underlying cardiac disease. In one participant [(b) (6)], acute pulmonary edema, while not directly related to study drug, resulted from complicated prolonged hospitalization due to severe symptomatic ARIA-E.

Respiratory failure/Acute respiratory failure

Four subjects [(b) (6)] had an SAE of respiratory failure or acute respiratory failure while receiving lecanemab in 301 Core, and one patient [(b) (6)]) during the 301 OLE. One occurred in the setting of pulmonary edema in the setting of cardiac disease ([(b) (6)]), three in the setting of obstructive lung disease with or without pneumonia [(b) (6)]). Subject [(b) (6)] with a relevant past medical history of chronic obstructive pulmonary disease, and exertional dyspnea at baseline, had three separate events of acute respiratory failure leading to hospitalization during participation in 301 Core. These occurred in the setting of advanced COPD exacerbation at times in the setting of a lung infection. See briefly history for [(b) (6)] under acute kidney injury.

Reviewer Comment: I could not identify a role of study drug in these instances.

Thoracic vertebral fracture

Two subjects ([(b) (6)]) on lecanemab during 301 Core experienced a thoracic vertebral fracture. The thoracic vertebral fracture in the case of [(b) (6)] occurred in the

setting of lymphoma, and in subject (b) (6), occurred in the setting of a seizure due to ARIA-E. See Section 12.1.4 for narratives.

Reviewer Comment: I reviewed these narratives and did not identify a direct role of study drug in these instances. In subject (b) (6) the thoracic vertebral fracture likely resulted from a seizure which was secondary to ARIA-E.

Rhabdomyolysis

(b) (6) is a 57-year-old male who experienced rhabdomyolysis on Study day 476, after he was found by a search and rescue team, extremely dehydrated with multiple cuts and abrasions on his body and taken to the hospital after one day of being in the wilderness alone and having encountered poor weather conditions (100 F).

Reviewer Comment: In this case rhabdomyolysis is likely related to being dehydrated and immobile for a prolonged period rather than study drug related.

Motor Neuron Disease

Subject (b) (6) is a 68-year-old male who received lecanemab during 301 Core. On Study day 57, he was noted to have fasciculations, and muscle atrophy but no weakness. On Study day 73 underwent EMG which was consistent with ALS. Study drug was discontinued permanently.

Reviewer Comment: Given the presence of motor neuron disease, early during the study course, and the latency for symptoms of motor neuron disease to manifest, I am unable to identify a role of study drug in motor neuron disease in this subject.

Death (sudden death)

Subject (b) (6) is an 85-year-old female randomized to LEC10-BW in Study 301 Core. See Section 12.1.3 for her narrative. The sponsor's narrative does not provide a cause of death or describe the circumstances leading to her death. The only other AE in the ADAE dataset during her study participation was abnormal dreams.

Reviewer Comment: *Given lack of information, I am unable to make a determination on the relatedness of the study drug to this patient's death.*

Narratives of SAEs occurring in ≥ 3 subjects receiving LEC10-BW during Core and/or OLE

These narratives include those that were not included under narratives for SAEs in 301 Core. SAEs that occurred in ≥ 3 subjects receiving LEC10-BW during Core, but did not occur in 2 or more subjects greater than placebo, and did not occur in 301 OLE will not be included in this section (such as SAE of transient ischemic attack).

Narratives of the following SAEs in the combined 301 Core and OLE period have been reviewed above based on SAEs narratives selected in 301 Core: infusion related reactions, ARIA-E, atrial

fibrillation, angina pectoris, Syncope, Acute myocardial infarction, ARIA-H, cerebral hemorrhage, COVID-19 pneumonia, diverticulitis, fall, noncardiac chest pain, subdural hematoma, hyponatremia.

The following SAEs were identified for occurring in 3 or more subjects during 301 OLE, and have not been covered earlier under narratives for SAEs selected based on 301 Core (because they did not occur in 2 or more subjects receiving LEC10-BW compared to placebo during the placebo controlled period): inguinal hernia, femoral neck fracture, hip fracture, transient ischemic attack, and pneumonia.

Pneumonia

Three subjects in 301 Core (b) (6) and 6 subjects in 301 OLE (b) (6)) had an SAE of pneumonia.

Reviewer Comment: I reviewed these narratives and could not identify a clear role of study drug in any of these cases, as pneumonia in individuals with dementia in this age group is not uncommon.

Inguinal Hernia

There were 3 subjects who had inguinal hernia during participation in 301 Core ((b) (6), and one subject (b) (6)), during 301 OLE. See Section 12.1.4 for narratives.

Reviewer Comment: I reviewed these narratives and did not identify a role of study drug in these events.

Fracture

In 301 Core, there were three subjects (b) (6)) with an SAE of hip fracture two ((b) (6)) with an SAE of femoral neck fracture. one subject (b) (6) with an SAE of femur fracture, one with rib and humerus fracture (b) (6)), two thoracic vertebral fractures (b) (6)), one wrist fracture (b) (6)), one ankle fracture (b) (6)), one upper limb fracture (b) (6)), one patella fracture (b) (6) and one forearm fracture (b) (6). In the 301 OLE there was one femoral neck fracture (b) (6)), three subjects had an upper extremity fracture; (b) (6) (upper limb fracture), (b) (6) (ulna fracture), (b) (6) (radius fracture), (b) (6) (humerus fracture), one pelvic fracture ((b) (6), and one cervical vertebral fracture (b) (6)).

Reviewer Comment: I reviewed these narratives and did not identify a clear role of study drug in most of these events; the falls were either mechanical (navigating electric tricycle on speed bumps, slipping, getting distracted by dog) or no clear explanation was found. The events did not occur proximal to an infusion or associated with ARIA except in two subjects in whom a

vertebral fracture occurred secondary to a seizure (b) (6)) or fall (b) (6)) which was secondary to ARIA.

Intentional Self injury/Suicide Attempt/Suicidal Ideation (Inclusive of 3 non- SAE events)

(b) (6)
73-year-old male on lecanemab with no past medical history of depression, on Study day 127 during the 301 Core, tried to shoot himself with his gun and was hospitalized to an inpatient psychiatric unit for intentional self-injury. He also sustained a subdural hematoma as a result. He was diagnosed with Major Depression, which was felt to be a single self-limited event, and the decision was that ongoing treatment for depression was not warranted. His psychotropic medications were adjusted while under observation in the hospital. This subject went on to complete study 301 Core and participation in 301 OLE is ongoing.

(b) (6)
58-year-old male with no past medical history of depression, who received lecanemab during the 301 Core, started to experience depression on extension day 179. He was treated with escitalopram. On extension day 180, he attempted suicide. He sustained minimal physical damage and had suicidal ideation for less than once a week, for fleeting few seconds or minutes, which he could control with some difficulty. The study drug was temporarily interrupted due to the event of suicide event. The narrative states that the suicide attempt resolved on the same day 180, and study drug was presumed on extension day 266. As of the cutoff of December 1, 2022, the subject was ongoing in the OLE study.

Reviewer Comment: While I cannot rule out a role of study drug with certainty, the fact that these subjects continued with study drug, and their participation is ongoing in the OLE, without recurrence of suicidal ideation of self-harm/suicide attempt a role of study drug in these events seems less likely.

(b) (6)
74-year-old male with past medical history of depressed mood, sustained an acute stroke on Study day 380, he was administered the C-SSRS in the ER (where he went for fatigue and hyponatremia). At that time he provided affirmative responses to suicidal ideation related questions. The subject died shortly after due to bronchogenic carcinoma with metastasis to the liver.

(b) (6)
62-year-old female with history of depression completed 301 core on placebo. On extension day 223, 12 days after the 16th dose of lecanemab, she reported suicidal ideation. No action was taken with study drug, and this was ongoing as of data cutoff of December 1, 2022.

(b) (6)

60-year-old male with past medical history of anxiety, but no history of depression, and at initial screening did report suicidal ideation of less than once a week for a few seconds, but on follow up screening did not report any suicidal behavior or ideation. He completed study 301 Core on placebo. On extension day 259, 12 days after the 12th dose of lecanemab, he reported to a neuropsychiatrist wanting to end his life and was stockpiling benzodiazepines. His study partner reported presence of suicidal ideation for 1.5 months. Patient's psychiatric medications were adjusted, and suicidal ideation resolved on extension day 898. Study drug was interrupted and restarted on extension day 275. His participation is currently ongoing.

(b) (6)

65-year-old male randomized to lecanemab in 301 Core. His past medical history did not include depression. At screening the subject did report suicidal ideation, at baseline assessment he had no suicidal behavior or ideation. On extension day 182, 20 days after the 13th dose of study drug during the OLE phase, he reported suicidal ideation. He was evaluated by a psychiatrist and his suicidal ideation was ongoing as of December 2, 2022.

Reviewer Comment: Since these subjects did report either a past medical history of depression or positive responses to suicidal ideation at screening or baseline, I cannot firmly confirm a role of study drug in these instances.

Table 37 SAEs by Preferred Term Occurring in 3 or more Subjects in 301 OLE

Preferred Terms	Lecanemab (N =1385)
Total Subjects with any Adverse Events	126 (9.1%)
Amyloid related imaging abnormality-oedema/effusion	11 (0.8%)
Infusion related reaction	10 (0.7%)
Amyloid related imaging abnormality-microhemorrhages and hemosiderin deposits	7 (0.5%)
Pneumonia	6 (0.4%)
Urinary tract infection	6 (0.4%)
Acute myocardial infarction	4 (0.3%)
Cerebrovascular accident	4 (0.3%)
Seizure	4 (0.3%)
COVID-19	3 (0.2%)
Cerebral hemorrhage	3 (0.2%)

Safety population and TRTEMFL = Y
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Table 38 SAEs by Preferred Term occurring in 3 or more Subjects on Lecanemab in 301 Core and OLE

Dictionary-Derived Term	N=1612 N(%)
Nervous System Disorders	**64(4.3)**
Amyloid related imaging abnormality-oedema/effusion	18(1.1)
Amyloid related imaging abnormality-microhemorrhages and hemosiderin deposits	9(1)
Syncope	8(0.5)
Cerebral hemorrhage	6(0.4)
Cerebrovascular accident	6(0.4)
Seizure	5(0.3)
Transient ischemic attack	5(0.3)
Injury poisoning and procedural complications	**54(3.4)**
Infusion related reaction	20 **(1.2)**
Fracture	24 (1.5)
Fall	5(0.3)
Subdural hematoma	5(0.3)
Infections and Infestations	**44(2.7)**
Pneumonia	9(1)
Urinary tract infection	7(0.4)
COVID-19	5(0.3)
COVID-19 pneumonia	4(0.2)
Diverticulitis	4(0.2)
Sepsis	3(0.2)
Cardiac Disorders	**33(2.1)**
Angina pectoris	8(0.5)
Atrial fibrillation	8(0.5)
Acute myocardial infarction	6().4)
Coronary artery disease	3(0.2)
General Disorders and Administration site conditions	**7(0.4)**
Non-cardiac chest pain	5(0.3)
Metabolism and nutrition disorders	**9(0.7(**
Hyponatremia	4(0.2)
Gastrointestinal disorders	**18(1.2)**
Inguinal hernia	4(0.2)
Musculoskeletal and connective tissue disorders	**9(06))**
Osteoarthritis	4(0.2)
Renal and urinary disorders	**8(0.5)**
Acute kidney injury	3(0.2)
Respiratory, thoracic and mediastinal disorders	**13(0.8)**
Acute respiratory failure	3(0.2)

Reviewer Created using the 90-Day updated ADAE dataset, lecanemab safety population=yes, treatment emergent flag=yes, open label treatment emergent=yes, and excluding if actual treatment during period 01=placebo, AND treatment emergent flag=yes. This data then was summarized by dictionary derived term, system organ class and unique subject ID.
Under the System Organ Class heading the numbers represent any subject who had one or more TEAE falling under that classification. Only preferred terms occurring under a SOC in 2 or more subjects on lecanemab and at higher frequency compared to placebo are listed.

12.1.5. SAE Narratives and Tables for 201 OLE, and ongoing Blinded Studies

Table 39 SAEs by Dictionary Derived Term in the Ongoing 201 OLE study Occurring in ≥ 2 Subjects and SAEs of Special Interest

Preferred Terms	Lecanemab(N = 180)
Total Subjects with any Adverse Events	50 (27.8%)
Cervical vertebral fracture/rib fracture/craniofacial fracture/femur fracture	7 (3.9)%)
Fall	5 (2.8%)
Acute kidney injury	3 (1.7%)
Transient ischemic attack	3 (1.7%)
Acquired epileptic aphasia/generalized tonic clonic seizure/seizure	3 (1.7%)
Atrial fibrillation	2 (1.1%)
COVID-19	2 (1.1%)
Cerebral infarction	2 (1.1%)
Chest discomfort	2 (1.1%)
Fracture	3 (1.1%)
Mental status changes	2 (1.1%)
Myocardial infarction	2 (1.1%)
Pneumonia	2 (1.1%)
Subdural hemorrhage/ subdural hygroma	2 (1.1%)
Amyloid related imaging abnormality-oedema/effusion	1 (0.6%)
Cerebral hemorrhage	1 (0.6%)
Infusion related reaction	1 (0.6%)
Superficial siderosis of central nervous system	1 (0.6%)
Syncope	1 (0.6%)

Safety population and TRTEMFL = Y
[tsae2.rtf] [tsae2.sas] 03MAY2023, 18:22
** fracture includes one femur fracture and two hip fractures*

201 OLE Narratives of SAEs which increased in incidence or are new compared to review of original submission:

The following new SAES or those with increased frequency in SAEs will be reviewed.

The incidence of SAEs for adverse events of interest; ARIA-E, superficial siderosis, cerebral hemorrhage has not changed since the previous review and will not be reviewed again here.

Falls

There were 5 subjects (b) (6)) who sustained an SAE of fall in study 201 OLE. All of these falls occurred at home. Subject (b) (6) fell off the stairs, on the day she received the 12th dose of study drug in 201 OLE.

Reviewer Comment: I reviewed these narratives all of which lacked detail as to the cause of the fall. The fact the falls occurred after multiple doses of the study drug, and most of the subjects continued to receive study drug without any further complications, makes it less likely that these are related to study drug.

Serious Fractures

In Study 201 OLE there were 11 subjects who had a serious fracture event: two subjects experienced rib fracture ((b) (6)), two experienced a hip fracture ((b) (6)), one a femur fracture ((b) (6)), three cervical vertebral fractures ((b) (6)). The events occurred due to falls, or accidents, and were not closely related to an infusion, or ARIA event. In two subjects the falls leading to the fracture occurred on the day of the infusion, but there was no clear indication in the narratives that there were other symptoms related to the infusion that led to the falls. One subject who had cervical vertebral fracture((b) (6)) due to a car accident, ultimately died due to prolonged hospitalization and spinal cord injury.

Reviewer Comment: I reviewed all of these narratives and could not identify a clear role of study drug, however I could also not entirely rule out a role of study drug in the falls in two participants in whom fall occurred on the day of an infusion

Subdural Hemorrhage/subdural hematoma/subdural hygroma

In study 201 OLE two subjects ((b) (6)) had an SAE of subdural hemorrhage. In subject (b) (6) it occurred as a result of a biking accident, and subject (b) (6) had subdural hygroma/subdural hematoma discovered during study MRI with no preceding events or symptoms, and likely due to advanced age. See Section 12.1.5 for detailed narratives.

Reviewer Comment: I could not identify a clear role of study drug in these instances.

For the ongoing blinded studies only SAEs for AESI will be briefly described or listed below. Other SAEs will not be listed due to the blinded nature of these events. This reviewer reviewed the blinded list of SAEs not related to ARIA, cerebral hemorrhage, infusion related reactions or

hypersensitivity in the ongoing blinded studies and there did not appear to be any clear new safety signals noted.

Ongoing Study 301 in China (study drug blinded)

There was one SAE (b) (6), in a patient who was an ApoE ε4 carrier who was not on an antithrombotic, and experienced ARIA-E and ARIA-H superficial siderosis and microhemorrhage on the day of the 13th dose of study drug administration with no action was taken with study drug, and five days after he received the 25th dose of study drug, he experienced dizziness, headache, gait and visual disturbance, and CT showed a "massive" 54 mm left occipital cerebral hemorrhage and increase in the size of the superficial siderosis. He was hospitalized and had prolonged hospitalization with complications, and another patient had 2 ARIA-H events (ARIA-H microhemorrhage and intracerebral hemorrhage, and symptomatic ARIA-H superficial siderosis ((b) (6)), symptomatic ARIA-H microhemorrhage, and ARIA-H macrohemorrhage, asymptomatic ARIA-H superficial siderosis ((b) (6)).)

Reviewer Comment: Given that the study is blinded and that ARIA and cerebral hemorrhage has been observed on placebo in this patient population no causality assessment can be made at this time.

Study 303 (A3 and A45) (Study Drug Blinded)

In Study 303 A3, there were no SAEs due to ARIA-E, ARIA-H, skin rash or other hypersensitivity reaction (including infusion related reaction).

In Study 303 A45, there were 2 SAEs reported: one ((b) (6)) related to severe, serious symptomatic ARIA-E and the other ((b) (6)) due to infusion related reaction. Both are described below.

(b) (6) is a 69-year-old female had one microhemorrhage at baseline, and after 3 or 4 doses of study drug experienced headaches, mild word finding problems and lightheadedness. Week 8 scan revealed severe ARIA-E and ARIA-H. She was hospitalized for severe, symptomatic and serious ARIA-E and received steroid treatment. It was reported that the imaging findings could also be consistent with PRES. She had 34 definite and 5 possible microhemorrhages as well as 29 definite and 4 possible superficial siderosis. Follow up MRI revealed 14 new microhemorrhages. According to the CIOMS, study drug was restarted after about 15 days of interruption, and another 15 days later steroids were stopped. It was reported that clinically she was doing well. Follow up MRI obtained a month after the original MRI showed that she sustained an additional 12 new microhemorrhages, and ARIA-E size was reduced. Four months after onset she recovered from severe symptomatic ARIA-E and study drug was withdrawn. She had acquired cumulatively 61 microhemorrhages during this period.

Reviewer Comment: This is a preclinical patient who sustained severe symptomatic ARIA-E with a high number of microhemorrhages, who had complete resolution of her clinical symptoms, and recovered from severe and serious ARIA-E without sequela. Whether she is continuing to receive study drug or not is unclear from the narrative. It is unclear if episodes of ARIA-E or accumulation of a relatively large number of microhemorrhages as in this case has any detrimental effects in individuals particularly, symptoms free, preclinical AD subjects. Similar to other ARIA-E events noted in several other subjects in the lecanemab clinical development program, the MRI reader has entertained PRES as a possible etiology, highlighting that radiographically ARIA-E and PRES may look very similar.

(b) (6)

74-year-old female in the A45 study sustained a Grade 2 infusion related reaction requiring hospitalization (serious) on the first day of infusion. Symptoms included feeling cold, shivering with upper back/neck tightness, and persistent fever for ~4 hours after infusion. Treated with paracetamol, chlorphenamine with resolution of symptoms the following day. No action was taken with study drug.

Other Study Drug Blinded SAEs from the ongoing 301 Core Study in China

I reviewed the study drug blinded SAE reports, for events that were not AESI, from the ongoing Study 303 and 301 Core Study in China. I did not identify a pattern of AEs that suggests a new safety signal.

12.1.6. Discontinuations in 301 Core and OLE, Tables and Narratives

Table 40 Study Withdrawals by Treatment Arm in Study 301 Core

301-CORE Summary of Exposed Subject Disposition by Arm

	Placebo (N=897)	10 mg/kg bi-Weekly (N=898)
Discontinued from Core Study	148 (16.5)	185 (20.6)
ADVERSE EVENT	30 (3.3)	54 (6.0)
LOST TO FOLLOW-UP	5 (0.6)	5 (0.6)
OTHER	19 (2.1)	22 (2.4)
WITHDRAWAL BY SUBJECT	94 (10.5)	104 (11.6)
Discontinued from Treatment	156 (17.4)	199 (22.2)

301-CORE Summary of Exposed Subject Disposition by Arm

	Placebo (N=897)	10 mg/kg bi-Weekly (N=898)
ADVERSE EVENT*	28(3.1)	65(7.2%)
LACK OF EFFICACY	1 (0.1)	0
LOST TO FOLLOW-UP	3 (0.3)	1 (0.1)
OTHER	24 (2.7)	27 (3.0)
WITHDRAWAL BY SUBJECT	99 (11.0)	102 (11.4)

ADDS.xpt, and ADAE.xpt*, OCS and review team created.

Narratives of Discontinuations in 301 Core

Amyloid related imaging abnormality-microhemorrhages and hemosiderin deposits

There were 15 subjects on lecanemab and 1 (b) (6)) in the placebo arm where study drug was withdrawn after occurrence of an ARIA-H microhemorrhage prior to completion of dosing in 301 Core. In most of these cases the subjects had concurrent ARIA-E and ARIA-H. Of the subjects on lecanemab in whom study drug was withdrawn for PT of ARIA-H microhemorrhage, 10/15 were ApoE e4 homozygotes (b) (6) were ApoE e4 heterozygotes. In 10 subjects (b) (6)) study drug was permanently discontinued due to ARIA-H microhemorrhage discontinuation criteria (any additional microhemorrhage after a subject cumulatively reaches 10 microhemorrhages). In 3 subjects discontinuation was due to a co-occurring ARIA-E and not directly due to ARIA-H (b) (6)), and in one ((b) (6)) it was due to superficial siderosis discontinuation criteria in and not due ARIA-H microhemorrhage or ARIA-E. There were 3 subjects in whom ARIA-H was symptomatic (b) (6)), and 2 in whom concurrent ARIA-E was symptomatic ((b) (6)) There was one subject in whom ARIA-H leading to discontinuation was an SAE (b) (6)). Noteworthy are 3 subjects who accumulated a large numbers of ARIA-H microhemorrhages as a result of study participation. The number of cumulative microhemorrhages, in those who were discontinued due to meeting protocol defined discontinuation criteria (n=16), ranged from 11 to 176 mean 45.5). Three subjects ((b) (6) with the highest number of microhemorrhages achieved will be described below briefly. All other narratives can be found in Section 12.1.9.

(b) (6)

86-year-old male who was ApoE ε4 homozygous randomized to receive lecanemab during 301 Core. He was not on antithrombotics per narrative. At the time of the screening MRI this subject did not have any superficial siderosis, macrohemorrhages, ARIA-E but had 4 new microhemorrhages located in the right frontal (3) and left frontal (1) area. He received the 4th

dose of lecanemab on study day 45. On Study day 45, MRI revealed a radiographically moderately severe ARIA-E in the right and left temporal regions as well as two new microhemorrhages for a total of 5 microhemorrhages. He remained asymptomatic. Study drug was held. On study day 73 MRI, ARIA-E was noted to have become radiographically severe, and there were 14 new microhemorrhages reported totaling 20 microhemorrhages. ARIA-H was reported to be clinically mild in severity. Lecanemab was restarted on study day 187. On study day 547 the subject was found to have 52 new microhemorrhages for a total of 72 microhemorrhages. At that time, he was also noted to have a new area of superficial siderosis in the left frontal region. He remained asymptomatic. On study day 606 a maximum of 27 new microhemorrhages were reported for a total of 99 microhemorrhages. Clinical severity was deemed to be mild. The study drug was permanently discontinued due to ARIA-H with the last dose taken on Study day 547.

(b) (6)

68-year-old female who was ApoE ε4 homozygous, who had one microhemorrhage at the screening MRI, and was on a baby aspirin. She received the 3rd dose of study drug on study day 28. On study day 44 there was report of worsening confusion, and poor vision. study day 50 MRI identified radiographically moderate ARIA-E in the left temporal, right parietal, left parietal, right occipital and left occipital regions. She also had 174 new microhemorrhages for a total of 175 microhemorrhages with 70 located in the occipital region, 10 located in the left temporal lobe, 15 located in the right parietal region, 50 located in the right occipital region and 30 located in the left parietal region. It was thought to be moderate in severity and symptomatic. On study day 180, a maximum number of 219 microhemorrhages were reported in the left parietal region, left temporal, right occipital right parietal, left occipital and left parietal regions. On study day 161, ARIA-H was unchanged. The treatment with study drug was permanently discontinued in response to ARIA-E and ARIA-H. The subject withdrew consent and discontinued study.

(b) (6)

70-year-old male who was ApoE ε4 homozygote, was not on an antithrombotic per narrative, and had one microhemorrhage on screening MRI. On study day 71, the subject received the 6th dose of study drug. On the same Day, MRI showed 23 new microhemorrhages for a total of 24 microhemorrhages. The subject was symptomatic with confusion and reduced visual acuity which were clinically rated as mild and nonserious. He also experienced a radiographically severe ARIA-E, it was also deemed to be symptomatic. Study drug was interrupted. On study day 78, one new microhemorrhage was reported for a total of 28 microhemorrhages. On study day 93, 24 new microhemorrhages for a total of 68 microhemorrhages was reported. On study day 98, 3 new microhemorrhages were reported for a total of 71 microhemorrhages. These were reported to be clinically mild, asymptomatic. The study drug was permanently discontinued with last dose taken on study day 71

Reviewer Comment: All three of these subjects had microhemorrhages at screening, were ApoE e4 homozygotes and had radiographically moderate or severe ARIA-E concurrent with ARIA-H. In these subjects, particularly subject (b) (6) who had 174 microhemorrhages, I cannot rule out underlying cerebral amyloid angiopathy, contributing to the ARIA-H events, during treatment with LEC10BW which may have exacerbated risk of bleeding with underlying CAA. This said, two other subjects who carried one or more e4 allele, who had 4 (b) (6)), and 2 (b) (6)) microhemorrhages at baseline had cumulative maximum number of 32 and 24 microhemorrhages consecutively.

Amyloid related imaging abnormality-edema/effusion

Fourteen discontinued study 301 Core due to a PT of ARIA-E, and one subject (b) (6) could not proceed to 301 OLE due to an AE of ARIA-E. Of these 10 (b) (6)) had concurrent ARIA -H (microhemorrhage or superficial siderosis) and are described under the narratives for ARIA-H discontinuations. Five subjects had ARIA-E leading to study drug discontinuation (with or without concurrent ARIA-H), three were homozygotes (b) (6)) 2 heterozygote (b) (6)) and one (b) (6)) was a noncarrier of the ApoE e4 allele). All of these were symptomatic, and four (b) (6)) were serious. In one subject (b) (6)) ARIA-H and associated symptoms came on 40 days after last dose of study drug, and do not meet the definition of treatment emergent, although this reviewer believes that the ARIA microhemorrhage that occurred while ARIA- E was radiographically present and the associated symptoms were study drug related. Subject (b) (6) who had severe symptomatic ARIA-E is described under Section 12.1.9 for narratives of these events.

Infusion Related Reactions

There were 12 subjects who received LEC10-BW and who discontinued due to infusion related reactions. Five were severe (b) (6) 5 were moderate (b) (6)) and 2 (b) (6)) were mild in severity. Six ((b) (6) were deemed to be serious. Standard toxicity grade was 2 in 5 subjects, Grade 3 in 6 subjects, and Grade 4 in one subject ((b) (6) This subject experienced an anaphylactic reaction with symptoms that involved two systems; the respiratory system (sibilance, dyspnea and CO_2 accumulation) and digestive system with persistent nausea and vomiting. Other symptoms described by subjects experiencing infusion related reaction included hypertensive urgency, nausea, vomiting, chills, shivering, back pain, muscle spasms, shortness of breath, and tachypnea, sleepiness and fatigue. Infusion related reaction leading to study drug discontinuation occurred in 8 subjects ((b) (6) after the first infusion, in three subjects after the second infusion (b) (6)), and in one subject (b) (6)) after the 7th infusion. One subject ((b) (6)) had a milder (Grade 1) reaction after the first infusion prior to

discontinuation after the second infusion. Most subjects who received an infusion related reaction were treated with anti-pyretic such as paracetamol, antihistamines such as diphenhydramine or chlorphenamine, and steroids and epinephrine in two cases. Those who had elevated blood pressure received agents to reduce their blood pressure. See Section 12.1.10 for narratives.

Superficial Siderosis

In four subjects study drug was discontinued for a PT of superficial siderosis, 2 ApoE e4 homozygotes ([(b) (6)],) and 2 ApoE e4 heterozygotes ([(b) (6)]). Subjects [(b) (6)] had concurrent ARIA-E and ARIA-H microhemorrhage. Subject [(b) (6)] was discontinued mainly due to the 99 microhemorrhages this subject accumulated cumulatively. Subject [(b) (6)] sustained a microhemorrhage on study day 43, and on study day 350 had a moderately severe symptomatic ARIA-E (with vertigo) as well as 2 microhemorrhages and superficial siderosis. Study Drug was permanently discontinued due to the event of symptomatic ARIA-E (not meeting protocol defined discontinuation criteria for ARIA-E or ARIA-H). Subjects [(b) (6)] had concurrent ARIA-E. Subject [(b) (6)] was discontinued after two events of moderately severe ARIA-E, both associated with ARIA-H (superficial siderosis). The first ARIA-E and superficial siderosis event was asymptomatic, and the second ARIA-E and ARIA-H event was symptomatic, with initial symptoms of right side of check numbness and tickling, and then acute headache while ARIA-E was still radiographically present. While there were not three occurrences of radiographically moderate ARIA-E events or symptomatic ARIA-E or ARIA-H (which are the per protocol discontinuation criteria), the subject was discontinued for two occurrences of symptoms associated with ARIA-E or ARIA-H. In subject [(b) (6)] it is stated that study drug discontinuation resulted from a PT of superficial siderosis and breast cancer. This subject had an initial event of superficial siderosis on study day 168 which presented with dizziness and balance problems. On Study day 202, they had a new area of superficial siderosis. On study day 351 the areas of superficial siderosis increased in size in the two locations but remained asymptomatic. There was no accompanying ARIA-E or ARIA-H microhemorrhage. Considering the increase in size as a third occurrence of superficial siderosis that was symptomatic, this would meet per protocol discontinuation criteria.

Depression

Two subjects [(b) (6)]) in the study drug arm discontinued due to a PT of depression. One [(b) (6)]), had a history of depression and the other ([(b) (6)]) did not. Both had onset of moderately severe depression during study participation. The narratives did not provide details of symptoms of depression leading to study discontinuation. In the case of subject [(b) (6)] who was 58 years old, it was stated that the other reason for discontinuation was that it was too difficult for the caregiver to bring him to appointments (as the caregiver was still working). None were reported to have suicidal ideation or behavior.

Discontinuations occurring in one subject receiving LEC10BW but include a TEAE of interest:

Subdural hematoma ([(b) (6)]): 81-year-old male was found to have a chronic subdural hematoma with brain compression incidentally on an MRI obtained on study day 259. He had no history of trauma preceding this and did not have any ARIA-E or ARIA-H during the course of the study. He underwent decompression surgery and study drug was permanently discontinued.

Reviewer Comment: While the occurrence of subdural hematoma has been infrequently observed in the setting of ARIA-E and ARIA-H, in this case, it is more likely that the subdural hematoma is due to age related brain atrophy and resulting and stretching and weakening of the bridging veins.

Thrombocytopenia ([(b) (6)]) and hypothermia ([(b) (6)]) were observed with a PT of infusion related reaction and were described earlier in this section under infusion related reactions.

Cerebral hemorrhage ([(b) (6)]): This subject was described under Section 12.1.9 under Serious Adverse Events.

Hypersensitivity [(b) (6)] described under Section 12.1.10 under Serious Adverse Events

Urticaria ([(b) (6)]): This subject received the 6th dose of study drug on study day 71. On study day 72 he experienced urticaria on chest, stomach, arms and legs which was moderate in severity and nonserious. No treatment was reported for this event, but he was permanently discontinued due to this event. Urticaria resolved on study day 79.

Table 41 Treatment Emergent Events Leading to Study Drug Discontinuation and Occurring in More than one Subject in Study 301 OLE

Preferred Terms	Lecanemab 10mg/bi-week (N =1385)
Total Subjects with any Adverse Events	57 (4.1%)
Amyloid related imaging abnormality-oedema/effusion	16 (1.2%)
Amyloid related imaging abnormality-microhemorrhages and hemosiderin deposits	11 (0.8%)
Infusion related reaction	11 (0.8%)
Cerebral hemorrhage	3 (0.2%)
Superficial siderosis of central nervous system	3 (0.2%)
Cerebrovascular accident	2 (0.1%)
Dementia Alzheimer's type	2 (0.1%)

Preferred Terms	Lecanemab 10mg/bi-week (N =1385)

Safety population and TRTEMFL = Y
[teaediscon4.rtf] [teaediscon4.sas] 08MAY2023, 13:19

Additionally the following TEAEs of interest led to study drug discontinuation during the OLE in one subject: brain neoplasm (glioblastoma), hypersensitivity, rash, seizure, subdural hematoma, thalamus hemorrhage.

Table 42 Treatment Emergent Events Leading to Study Drug Discontinuation and Occurring in More than One Subject in Study 301 OLE + Core

Preferred Terms	Lecanemab (N =1612)
Total Subjects with any Adverse Events	124 (7.7%)
Amyloid related imaging abnormality-oedema/effusion	31 (1.9%)
Amyloid related imaging abnormality-microhemorrhages and hemosiderin deposits	27 (1.7%)
Infusion related reaction	23 (1.4%)
Superficial siderosis of central nervous system	7 (0.4%)
Cerebral hemorrhage	4 (0.2%)
Cerebrovascular accident	3 (0.2%)
Dementia Alzheimer's type	2 (0.1%)
Depression	2 (0.1%)
Hypersensitivity	2 (0.1%)
Myocardial infarction	2 (0.1%)

Safety population and TRTEMFL = Y
[teaediscon2.rtf] [teaediscon2.sas] 26APR2023, 07:54

301 OLE Summary of TEAES leading to study discontinuation

Infusion Related Reactions:

Eleven subjects (b) (6)) experienced a PT of infusion related reaction which led to study drug discontinuations during the 301 OLE study. All, but one (b) (6)), had received placebo in the Core. The Infusion related reaction occurred at the time of the first infusion in most of these subjects except for subject (b) (6) , who had received 40 doses of lecanemab, and subject (b) (6) who had received 2 doses of lecanemab. Of these 6 (b) (6) were serious. Severity assignment was moderate for 9, severe for two ((b) (6)), and mild for one subject

(b) (6)). Toxicity grading assigned was 3 for three subjects ((b) (6) and was Grade 2 for all others. Symptoms and signs consisted of chills, shivering, shaking, dizziness, feeling cold, feeling faint, hypothermia, flushing in the chest, fevers, nausea, vomiting, headache, hypotension, tachypnea, low oxygen saturation. Some patients were treated with antipyretics, diphenhydramine or other antihistamine, antinausea medications, or steroids. In most cases symptoms resolved by the next day. See Section 12.1.10 for details related to these discontinuations.

ARIA-E

There were 16 subjects on lecanemab who had a TEAE of ARIA-E that led to study drug discontinuation during the OLE. 7 were ApoE ε4 homozygotes (b) (6) and 7 ApoE ε4 heterozygotes ((b) (6)), and 2 were noncarriers (b) (6)). Of these 9 ((b) (6)) were serious events. In 6/16 outcome was recovered/resolved, in 9/16 outcome was not recovered /not resolved, in 2/16 outcome was recovering /resolving and in one outcome was recovered with sequela. Thirteen out 16 of the ARIA-E events leading to study drug discontinuation during the 301 OLE were symptomatic and 4 out of 16 (b) (6)) were not symptomatic. See Section 12.1.9 for details

ARIA-H-microhemorrhage

Eleven subjects ((b) (6) iscontinued due to ARIA-H during the OLE study. Of these 4 were serious (b) (6) and 3 were symptomatic (b) (6)). 4 had concurrent symptomatic ARIA-E (b) (6)) and two had concurrent asymptomatic ARIA- E (b) (6)) Radiological severity was severe (>10 microhemorrhages) in 8 subjects, meeting study discontinuation criteria, , mild in two ((b) (6)) and moderate in one ((b) (6)). See Section 12.1.9 for details.

ARIA-H superficial siderosis

There subjects ((b) (6)) had study drug discontinuation due to superficial siderosis in the 301 OLE. Radiographic severity was mild in 1/3, moderate in one and severe in one. None were deemed to be serious, or symptomatic. Two were associated with asymptomatic ARIA-E. Subject (b) (6) also had ARIA-H microhemorrhage, cerebral hemorrhage and radiographically severe ARIA-E (co-localized). Subject (b) (6) was discontinued for ARIA-H microhemorrhage and superficial siderosis. Subject (b) (6) was discontinued for superficial siderosis occurring after 5th dose of study drug during the extension period. He remained asymptomatic.

The following discontinuations occurred in one subject each in the 301 OLE based on the ADAE dataset with data cutoff of December 1, 2022: Cerebral hemorrhage (n=3) (b) (6)

(b) (6) Hypersensitivity (b) (6)), Rash (b) (6)), seizure ((b) (6) and Thalamus hemorrhage ((b) (6)

One subject ((b) (6)) experienced a TEAE of hypersensitivity which led to study drug discontinuation. This subject received placebo during 301 Core. On extension day 30, a day after she received the second dose of study drug, she developed a fever (38°C) and purpura in both lower extremities. The event was classified as moderate in severity and nonserious. The subject presented to the emergency room on extension day 30 and underwent a skin biopsy on study day 36. Study drug was permanently discontinued due to the event of hypersensitivity with the last dose taken on extension day 29. The event of hypersensitivity resolved on extension day 36.

Subject (b) (6) experienced a rash that led to study drug discontinuation. This subject received LEC10BW during 301 Core. On study day 475 the subject experienced a rash, and was treated with diphenhydramine and paracetamol. No action was taken with study drug and the subject entered OLE, and on study day 2, a day after the first infusion in the OLE he experienced a rash, Study drug was permanently discontinued due to the rash.

201 OLE

In Study 201 OLE safety related criteria for discontinuation of study drug are as follows:
• Infusion reactions associated with administration of study drug, of Grade 3 severity or above (as defined in the NCI-CTCAE) that do not lessen or resolve with treatment
• Clinical features which indicate meningoencephalitis (e.g., combination of 1 or more of the following: headache, worsening confusion, neck stiffness, impaired consciousness, focal neurological signs)
• Hypersensitivity reactions with clinical features of tissue injury (e.g., arthritis, glomerulonephritis, mononeuritis multiplex)

As of December 1, 2022, 8/180 (4.4%) of subjects discontinued study drug due to a TEAE, compared to 7/180 compared to the original review. (Source 201 OLE CSR Table 14.3.1.2.1).

Two subjects had 2 TEAEs leading to study drug discontinuation (road traffic accident and subdural hemorrhage in one subject), and malignant neoplasm of unknown primary site and neuroendocrine carcinoma) in another subject.

The following 7 TEAE-related study discontinuations were already reviewed as part of the original BLA submission and will not be reviewed again: pancytopenia (b) (6), metastatic breast cancer (b) (6)), road traffic accident and subdural hemorrhage (b) (6), cervical vertebral fracture (b) (6)), infusion related reaction (b) (6)), malignant neoplasm of unknown primary and neuroendocrine carcinoma (b) (6)) and aggression (b) (6). Except infusion related reaction none were deemed to be related to study drug. There was one

additional TEAE leading to study drug discontinuation which was bilateral pneumonia consistent with COVID 19 (b) (6)) which also did not appear to be study drug related.

Study 301 Core-China (ongoing and study drug blinded)
In the ongoing, study drug blinded 301 Core study in China, there was one subject (b) (6) who discontinued study drug due to symptomatic cerebral hemorrhage, ARIA-H microhemorrhage, and ARIA-H superficial siderosis. Based on MRI reports subject sustained cumulatively 50 microhemorrhages and had a cerebral hemorrhage of 12 mm in the right temporal lobe, and superficial siderosis in the right frontal area, with the cerebral hemorrhage reducing in size over time.

Study 303 (ongoing and study drug blinded)
There were no study drug discontinuations in the 303 A3 trial (source: sponsor Listing 16.2.7.5). In the 303 A45 study the following TEAEs led to study drug discontinuation: Severe symptomatic ARIA-E ((b) (6) , invasive ductal breast cancer (b) (6) See the Section 12.1.5 for the narrative for subject (b) (6) with severe, symptomatic ARIA-E. Due to the blinded nature of study drug, narrative for (b) (6) will not be presented.

12.1.7. Treatment Emergent Adverse Events Additional Information

Discussion related to TEAEs by Body System or Organ Class System

The difference between lecanemab and placebo under the body system or organ class system of nervous system disorders was mostly driven by the higher number of subjects who experienced ARIA-E, ARIA-H, headache and superficial siderosis, where the lecanemab arm had 28-98 more subjects compared to placebo, and the following dictionary derived terms with 4-6 more subjects in the lecanemab arm compared to placebo: balance disorder, cerebral hemorrhage, syncope, tremor and tension headache. Similarly, the injury, poisoning and procedural complications SOC was driven by infusion related reactions (in 172 more subjects on lecanemab compared to placebo), and the following TEAEs that occurred in 4 or more subjects on lecanemab: fall, radius fracture, humerus fracture and muscle strain. The infections and infestations was driven by the following PTs, where the lecanemab arm had 4 or more subjects than the placebo arm: bronchitis, upper respiratory infection, cystitis, viral infection, cellulitis, gastroenteritis, tooth abscess, pharyngitis and influenza. Under the General disorders and administration site conditions the difference between the lecanemab arm and placebo, was driven by the following PTs in descending order, occurring in 4-13 more subjects in the lecanemab arm was driven by higher incidence of TEAEs fatigue, chills, feeling cold, infusion site extravasation, peripheral edema, pyrexia, and noncardiac chest pain. Under investigations, the most common AEs which occurred in 4 or more subjects in the lecanemab arm compared to the placebo in descending order were electrocardiogram QT prolongation, ALT and AST elevation, and SARS-voC2 test positive. Under the Cardiac Disorders POS, the following were observed in 4 or more subjects on the LEC10BW arm compared to placebo, in descending order: atrial fibrillation, angina pectoris, left bundle branch block, palpitations, atrioventricular block first

degree and sinus bradycardia/bradycardia. Under Neoplasms benign, malignant and unspecified (incl cysts and polyps) the following PTs were observed in more than 4-5 subjects on lecanemab arm compared to placebo in descending order: basal cell carcinoma, lipoma, squamous cell carcinoma. Renal and Urinary Disorder related PTs were mostly driven by hematuria and by acute kidney injury that occurred in 14 and 5 more subjects, respectively, receiving lecanemab.

Table 43 Incidence of Treatment Emergent Adverse Events by Organ System in 301 Core

Preferred Terms	Placebo (N = 897)	Lecanemab (N = 898)
Total Subjects with any Adverse Events	737 (82.2%)	800 (89.1%)
Nervous system disorders	292 (32.6%)	392 (43.7%)
Injury, poisoning and procedural complications	256 (28.5%)	372 (41.4%)
Infections and infestations	283 (31.5%)	327 (36.4%)
Musculoskeletal and connective tissue disorders	215 (24.0%)	218 (24.3%)
Gastrointestinal disorders	190 (21.2%)	197 (21.9%)
General disorders and administration site conditions	122 (13.6%)	172 (19.2%)
Psychiatric disorders	160 (17.8%)	144 (16.0%)
Skin and subcutaneous tissue disorders	104 (11.6%)	125 (13.9%)
Investigations	91 (10.1%)	104 (11.6%)
Vascular disorders	85 (9.5%)	91 (10.1%)
Respiratory, thoracic and mediastinal disorders	85 (9.5%)	89 (9.9%)
Cardiac disorders	62 (6.9%)	86 (9.6%)
Metabolism and nutrition disorders	78 (8.7%)	82 (9.1%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	58 (6.5%)	77 (8.6%)
Renal and urinary disorders	57 (6.4%)	69 (7.7%)
Eye disorders	65 (7.2%)	59 (6.6%)
Ear and labyrinth disorders	24 (2.7%)	31 (3.5%)
Immune system disorders	22 (2.5%)	29 (3.2%)
Blood and lymphatic system disorders	38 (4.2%)	28 (3.1%)

Safety population and TRTEMFL = Y
[teae1.rtf] [teae1.sas] 21APR2023, 15:25

Table 44 Preferred Terms Captured Under MQG Rash in 301 Core

Dictionary-Derived Term	Placebo	Lecanemab
ACNE	0	1
DERMATITIS	4	2
ERYTHEMA	1	6
ERYTHEMA MIGRANS	2	1
INFUSION SITE RASH	0	3
INJECTION SITE RASH	0	1
PEMPHIGOID	1	0
RASH	17	31
RASH ERYTHEMATOUS	0	1
RASH MACULAR	2	0
RASH MACULO-PAPULAR	2	0
RASH PAPULAR	2	0
RASH PRURITIC	0	2
SKIN EXFOLIATION	3	0
SKIN IRRITATION	2	2
SKIN REACTION	0	1
URTICARIA	3	5

Reviewer created using adae.xpt

Table 45 Incidence of TEAEs by Selected* Medical Query Groups Occurring 2% or Higher on Lecanemab and 2 % or Higher Compared to Placebo in Study 301 Core[Error! Bookmark not defined.]

FDA Medical Query Group	Placebo N= 897 N (%)	LEC10-BW N =898 N (%)
Dyspepsia FDA B	39 (4.3%)	54 (6.0)
Nausea vomiting MQG	37 (4.1%)	50 (5.6%)
Supraventricular tachycardia MQG	19 (2.1%)	33 (3.7%)
Infection viral MQG	13 (1.4%)	26 (2.9%)

Safety population and TRTEMFL = Y
[taeef1.rtf] [taeef1.sas] 12APR2023, 12:2

The incidence of designated medical events was too small to reach any firm conclusions. but did not appear to occur at a consistently higher incidence in the drug arms. (Table 46). Of those that had narratives (see Section 7.4.2 SAE), I did not identify a clear role of the study drug.

The incidence of the TEAEs in the Core and OLE combined dataset is provided in Table 49 . The incidence of infusions reactions (24%), ARIA-H (16%) and of ARIA-E (14%) in subjects on lecanemab in the combined 301 Core and OLE dataset were comparable to the incidence of those reactions in the 301 Core Study.

Table 46 Incidence of Treatment Emergent Designated Medical Events by Dictionary Derived Term Occurring in More Subjects on Lecanemab Compared to Placebo in Study 301 Core[Error! Bookmark not defined.]

Designated Medical Events by preferred term	LEC10-BW N =898 N (%)	Placebo N= 897 N (%)
Drug induced liver injury	1 (0.1)	0
Electrocardiogram QT prolonged	6 (0.7)	0
Rhabdomyolysis	1 (0.1)	0
Seizure/Partial Seizure	3 (0.3)	2(0.2)
Acute kidney injury/renal failure	9 (1)	5 (0.6)

Reviewer created table using the MedDRA Based Adverse Event (MAED) program to analyze the Study 301 ADAE dataset, selected for Study SAFFL=Y, TRTEMFL =Y, Open Label Extension Flag=" ".subjects who had a seizure in the setting of ARIA-E in the LEC10-BW group is not captured in this table, as the applicant did not include clinical symptoms of ARIA-E as separate TEAEs in the Adverse Events Dataset.

The event of drug induced liver injury was not an event that qualified for description in a narrative, as it was nonserious, and mild in severity. It occurred after the 7th dose of study drug, no action was taken with study drug, and it resolved. The subject went on to complete study..

TEAEs 301 Core and OLE

In all lecanemab treated subjects including those that received lecanemab during 301 Core only, those that received lecanemab both during Core and OLE, and those that only received lecanemab during the 301 OLE the overall incidence of TEAEs were 86.2% (1289 out of 1612). based on the 90-day updated ADAE dataset. The incidence of the most common TEAEs were similar to that observed during 301 Core alone: infusion related reactions reported in 395(24%) of the subjects, ARIA-H in 16%, and ARIA-E in 14%, and headache (10%) (Table 47.). The incidence of infusion related reactions, and ARIA-E and ARIA-H are comparable to the incidences of 26%, 14% and 13% respectively observed in 301 Core. Similar to the findings in the original review of 201 Core, the incidence of falls in 301 Core was not greater in lecanemab than in placebo, and that the incidence of falls in the 301 Core and OLE combined is within the reported rate of 29% for adults at least 65 years old in the general population reporting at least 1 fall in the previous year. [26]

Table 47 Incidence of TEAEs by Preferred Term During the 301 OLE Period.

Preferred Terms	Lecanemab (N =1385)
Total Subjects with any Adverse Events	1020 (73.6%)
Infusion related reaction	182 (13.1%)

[26] Bergen G, Stevens MR, Burns ER. Falls and Fall Injuries Among Adults Aged ≥65 Years — United States, 2014. MMWR Morb Mortal Wkly Rep 2016;65:993–998. DOI: http://dx.doi.org/10.15585/mmwr.mm6537a2external icon

Preferred Terms	Lecanemab (N =1385)
COVID-19	178 (12.9%)
Amyloid related imaging abnormality-microhemorrhages and hemosiderin deposits	159 (11.5%)
Amyloid related imaging abnormality-oedema/effusion	110 (7.9%)
Headache	78 (5.6%)
Fall	77 (5.6%)
Urinary tract infection	64 (4.6%)
Superficial siderosis of central nervous system	47 (3.4%)
Back pain	45 (3.2%)
Dizziness	43 (3.1%)
Arthralgia	42 (3.0%)
Nasopharyngitis	41 (3.0%)
Contusion	31 (2.2%)
Diarrhea	31 (2.2%)

Safety population and TRTEMFL = Y
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Table 48 Incidence of TEAEs by Primary Organ System Occurring at a Frequency of ≥ 5 % in Study 301Core and OLE Combined

	N=1612 N(%)
Nervous system disorders	697(43.2)
Infections and infestations	642(39.8%)
Injury Poisoning and procedural complications	639 (39.6)
Musculoskeletal and connective tissue disorders	368(22.8(
Gastrointestinal disorders	331(20.5)
General disorders and administration site conditions	277(17.2)
Psychiatric Disorders	260(16.1%)
Skin and subcutaneous tissue disorders	203(12.6%)
Investigations	183(11.4%)
Respiratory, thoracic and mediastinal disorders	156(9.7)
Renal and urinary disorders	129(8%)

Vascular disorders	152(9.4%)
Cardiac Disorders	122 (8.3%)
Neoplasms benign, malignant and unspecified	127(7.9)
Eye disorders	103(6.4%)

Sources: adae.xpt, reviewer created

Table 49 Incidence of TEAEs by Dictionary Derived Term at a Frequency of ≥ 5 % in Study 301 Core and OLE Combined

Dictionary Derived Term	N=1612 N(%)
Total Subjects with any Adverse Events 1389 (86.2%)	**1389 (86.2%)**
Infusion related reaction	395 (24.5%)
Amyloid related imaging abnormality-microhemorrhages and hemosiderin deposits	258 (16.0%)
COVID-19	237 (14.7%)
Amyloid related imaging abnormality-edema/effusion	219 (13.6%)
Headache	166 (10.3%)
Fall	158 (9.8%)
Urinary tract infection	134 (8.3%)
Back pain	103 (6.4%)
Superficial siderosis of central nervous system	96 (6.0%)
Arthralgia	94 (5.8%)
Dizziness	91 (5.6%)
Diarrhea	77 (4.8%)

Safety population and TRTEMFL = Y
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Table 50 Incidence of Treatment Emergent Severe Adverse Events in 301 OLE Occurring in 2 or More Subjects.

Preferred Terms	Lecanemab (N =1385)
Total Subjects with any Adverse Events	70 (5.1%)
Amyloid related imaging abnormality-oedema/effusion	10 (0.7%)
Infusion related reaction	7 (0.5%)
Cerebrovascular accident	4 (0.3%)
Amyloid related imaging abnormality-macrohemorrhages and hemosiderin deposits	2 (0.1%)
COVID-19 pneumonia	2 (0.1%)
Dementia Alzheimer's type	2 (0.1%)
Headache	2 (0.1%)

Preferred Terms	Lecanemab (N =1385)
Pneumonia	2 (0.1%)
Seizure	2 (0.1%)
Subdural hematoma	2 (0.1%)
Urinary tract infection	2 (0.1%)
Acute myocardial infarction	1 (0.1%)

Safety population and TRTEMFL = Y
[teaesev4_2.rtf] [teaesev4_2.sas] 16MAY2023, 09:32

Table 51 Incidence of TEAEs by Dictionary Derived Term at a Frequency of ≥ 5 % in Study 201 OLE

Preferred Terms	Lecanemab (N = 180)
Total Subjects with any Adverse Events	171 (95.0%)
Fall	44 (24.4%)
Infusion related reaction	38 (21.1%)
Urinary tract infection	28 (15.6%)
Fracture	28 (15.6)
COVID-19	25 (13.9%)
Amyloid related imaging abnormality-microhemorrhages and hemosiderin deposits	24 (13.3%)
Arthralgia	19 (10.6%)
Nasopharyngitis	19 (10.6%)
Anxiety	17 (9.4%)
Headache	16 (8.9%)
Upper respiratory tract infection	16 (8.9%)
Amyloid related imaging abnormality-oedema/effusion	15 (8.3%)
Back pain	15 (8.3%)
Fracture	
Contusion	15 (8.3%)
Hypertension	15 (8.3%)

Preferred Terms	Lecanemab (N = 180)
Dizziness	12 (6.7%)
Skin laceration	12 (6.7%)
Basal cell carcinoma	11 (6.1%)
Depression	11 (6.1%)
Nausea	11 (6.1%)
Vomiting	11 (6.1%)
Pyrexia	10 (5.6%)
Agitation	9 (5.0%)
Hypotension	9 (5.0%)
Skin abrasion	9 (5.0%)
Rash	5 (2.8%)
Seizure	4 (2.2)

Safety population and TRTEMFL = Y
>2% AE of Lecanemab group
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Reviewer modified; 1) fracture is sum of different types of PTs for fracture (i.e. femur fracture, thoracic vertebra fracture etc). 2) seizure includes one of each of the following PTs; acquired epileptic aphasia, focal dyscognitive seizure, generalized tonic clonic seizure, seizure.

12.1.8. ARIA Definitions and Management

ARIA-E and ARIA-H Definitions in Study 301

The applicant provided the following descriptions based on MedDRA terms for ARIA-E and ARIA-H and macrohemorrhage (. Note that the Division is not considering macrohemorrhage under ARIA-H but as a separate entity.

Table 52 Preferred Terms for ARIA-E and ARIA-H

Category Subcategory	Preferred Term-MedDRA: 25.0
ARIA-E[a]	Amyloid related imaging abnormality-oedema/effusion
ARIA-H[a]	
Macrohemorrhage	Cerebral haemorrhage Haemorrhage intracranial Thalamus haemorrhage
Superficial siderosis	Superficial siderosis of central nervous system
Cerebral microhemorrhage	Amyloid related imaging abnormality- microhemorrhage and hemosiderin deposit Cerebellar microhaemorrhage

ARIA-E = amyloid-related imaging abnormality-edema/effusion, ARIA-H = amyloid-related imaging abnormality-hemorrhage. a: Not considered as an ARIA event in 301 if the investigator reports "Other MRI abnormalities" instead of "ARIA-E" or "ARIA-H" for the case in category II study specific events CRF.
MedDRA Version 25.0
Source: BLA Seq 0002 ISS SAP Appendix 13.2

Reviewer Comment: Based on synonym search of MedDRA Version 25 the term amyloid related imaging abnormality-microhemorrhage and hemosiderin deposit was determined to be synonymous with and includes brain stem microhemorrhage, cerebral hemorrhage and cerebellar hemorrhage, and is consistent with definition of ARIA-H microhemorrhage in the original BLA761259 review and the aducanumab review

ARIA-E and ARIA-H Radiographic Classification in Study 301
The Applicant's radiographic severity for ARIA-E is described in Table 53 and Table 54(revised per Amendment 12).

Table 53 Radiographic Severity Assessment of ARIA-E in Study 301

Radiographic Severity		
Mild	**Moderate**	**Severe**
FLAIR hyperintensity confined to sulcus and/or cortex/subcortex white matter in one location <5 cm	FLAIR hyperintensity 5-10 cm in single greatest dimensions, or more than 1 site of involvement, each measuring <10 cm	FLAIR hyperintensity >10 cm with associated gyral swelling and sulcal effacement. One or more separate/independent sites of involvement may be noted.

FLAIR = Fluid Attenuating Inversion Recovery.
Source: Study 301 Core CSR.Appendix 16.1.1, Table 6, Study 201 Core CSR.Appendix 16.1.1, Appendix 4.

Table 54 Radiographic Severity Assessment of ARIA-H in Study 301

Radiographic Severity			
ARIA-H Type	**Mild**	**Moderate**	**Severe**
Cerebral microhemorrhage	≤4 new incident microhemorrhages	5-9 new incident microhemorrhages	≥ 10 new incident microhemorrhages
Superficial siderosis	1 focal area of superficial siderosis	2 focal area of superficial siderosis	>2 focal area of superficial siderosis

Source: BLA Seq 0002 ISS SAP Section 3.3.3.2.

ARIA Management

During the original review of BLA761269, because 201 Core ARIA management criteria required discontinuation for all cases of ARIA except for asymptomatic cerebral microhemorrhage, there was limited experience with dosing through multiple ARIA events**.** While Study 301 Core provides additional information of continued dosing (with or without interruption) in patients who experience ARIA-E, the number of multiple ARIA events was still too small to draw any firm conclusions. In 301 Core, dosing was continued for asymptomatic, radiographically mild ARIA-E, temporarily stopped for any symptomatic ARIA-E or radiographically moderate or severe ARIA-E (regardless of symptoms). Study drug could be resumed after resolution clinical symptoms and radiographical resolution of ARIA-E. This could be only repeated 2 times. Study drug was permanently stopped for serious symptomatic ARIA-E.

Table 55 Management of ARIA-E in Study 301

Symptoms of Radiology Findings	Study Drug Action	Required Follow-Up Safety Visits with MRI	Resumption of Treatment
Asymptomatic, radiographically mild	None	At approximately 30, 60, and 90 days (as unscheduled or scheduled visits) after the event was identified, then an MRI will be performed as per Schedule of Assessments.	N/A
Symptomatic or radiographically moderate or severe	Study drug temporarily stopped at 1st and 2nd occurrence in the study (ie, Core and OLE Phase)[a]. Study drug must be discontinued after the 3rd occurrence in the study (ie, Core and OLE Phase).	At approximately 30 days, then 90 days (as unscheduled or scheduled visits) after first identification, and every 30 days (as unscheduled or scheduled visits) until the ARIA-E has resolved radiologically or clinically.	Resumption of the treatment when resolved radiologically and clinically. Can occur a total of 2 times during the course of the treatment (ie, Core and OLE Phase).
Severe ARIA-E associated with SAE	Permanent discontinuation, report as SAE.	At approximately 30 and 90 days (as unscheduled or scheduled visits) after first identification. If not resolved, every 30 days until the ARIA-E has resolved radiologically or clinically.	No rechallenge permitted.

ARIA-E = amyloid-related imaging abnormality edema/effusion, MRI = magnetic resonance imaging, N/A = not applicable, OLE = extension phase, SAE = serious adverse event.
a: During treatment interruption, subjects should undertake all regularly scheduled assessments as described in the Schedule of Assessments.
Source: Study 301 Core CSR Appendix 16.1.1 Table 6.

In Study 301 Core, study drug could be resumed for asymptomatic microhemorrhages or superficial siderosis. For symptomatic microhemorrhages, superficial siderosis or single macrohemorrhage (regardless of whether symptomatic or not), study drug would be stopped

temporarily and resumed after resolution of symptoms and stabilization of radiological findings. This could only occur twice. If a subject cumulatively sustained > 10 microhemorrhages, the study drug would be temporarily stopped and restarted after stabilization of imaging/resolution of symptoms; however, if the subject continued to accrue more microhemorrhages after resumption study drug would be permanently discontinued. (**Table 56**)

Table 56 Management of ARIA-H in Study 301 Core

Symptoms of Radiology Findings	Study Drug Action	Required Follow-Up Safety Visits with MRI	Resumption of Treatment
Asymptomatic microhemorrhages	None	None	N/A
Asymptomatic superficial siderosis	None	None	N/A
Symptomatic microhemorrhages	Study drug temporarily stopped at 1st and 2nd occurrence in the study (ie, Core and OLE Phase)[a]. Study drug must be discontinued after the 3rd occurrence in the study (ie, Core and OLE Phase).	At approximately 30 days (as unscheduled or scheduled visits) after the event was identified. Further safety visits (with MRI) will occur at approximately every 30 days (as unscheduled or scheduled visits) until the event has stabilized radiographically and symptoms have resolved.	Treatment may resume upon resolution/stabilization of events. Resumption of treatment following the occurrence of events can only occur a total of twice during the Core and OLE Phase.
Symptomatic superficial siderosis	Study drug temporarily stopped at 1st and 2nd occurrence in the study (ie, Core and OLE Phase)[a]. Study drug must be discontinued after the 3rd occurrence in the study (ie, Core and OLE Phase).	At approximately 30 days after the event was identified. Further safety visits (with MRI) will occur at approximately every 30 days (as unscheduled or scheduled visits) until the event has stabilized radiographically and symptoms have resolved.	Treatment may resume upon resolution/stabilization of events. Resumption of treatment following the occurrence of events can only occur a total of twice during the Core and OLE Phase.
Single macrohemorrhage (>10 mm), symptomatic or not	Study drug temporarily stopped at 1st and 2nd occurrence in the study (ie, Core Study and OLE)[a]. Study drug must be discontinued after the 3rd occurrence in the study (ie, Core and OLE Phase).	At approximately 30 days (as unscheduled or scheduled visits) after the event was identified. Further safety visits (with MRI) will occur at approximately every 30 days (as unscheduled or scheduled visits) until the event has stabilized radiographically and symptoms have resolved.	Treatment may resume upon resolution/stabilization of events. Resumption of treatment following the occurrence of events can only occur a total of twice during the Core and OLE Phase.
Multiple (>10) microhemorrhages cumulatively, (symptomatic or not)	Study drug temporarily stopped at 1st occurrence in the study (ie, Core and OLE Phase)[a]. For subjects who already have ARIA-H of >10 cerebral microhemorrhages, should further new microhemorrhages develop after resumption of treatment at any time during the study (ie, Core or OLE Phase), the subject must be discontinued from the study drug.	At approximately 30 days (as unscheduled or scheduled visits) after the event was identified. Further safety visits (with MRI) will occur at approximately every 30 days (as unscheduled or scheduled visits) until the event has stabilized radiographically and symptoms have resolved.	Can occur only once during the course of the treatment (Core or OLE Phase).

ARIA-H = amyloid-related imaging abnormality hemorrhage, MRI = magnetic resonance imaging, N/A = not applicable, OLE = extension phase.
a: During treatment interruption, subjects should undertake all regularly scheduled assessments as described in the Schedule of Assessments.
Source: Study 301 Core CSR Appendix 16.1.1 Table 5.

201 OLE

In the ongoing 201-OLE study, safety MRIs are performed at OLE Baseline and at OLE Weeks 9, 13, and 27, (prior to the 5th dose, the 7th dose, and the 11th dose) and every 6 months thereafter. Management of ARIA-E in the 201-OLE is shown in the table below. Unlike the 301 Core where study drug was permanently discontinued after a symptomatic serious ARIA-E, in 201 OLE these subjects could continue dosing, after temporarily stopping dosing, and monitoring for clinical and radiographical resolution (Table 57).

Table 57 Management of ARIA-E in 201 OLE

Clinical Symptoms	ARIA -E Severity on MRI		
	Mild	Moderate	Severe
Asymptomatic	Continue dosing	Continue dosing [a]	Temporarily stop dosing until radiographic resolution
Symptomatic (any severity)	Temporarily stop dosing until radiographic resolution and resolution of symptoms	Temporarily stop dosing until radiographic resolution and resolution of symptoms	Temporarily stop dosing until radiographic resolution and resolution of symptoms

[a] Dosing is temporarily stopped in Japan for asymptomatic, radiographically moderate ARIA-E until radiographic resolution.

Resumption of treatment following symptomatic and/or radiographically moderate or severe ARIA-E could only occur twice, after which the subject was to be discontinued from the study. (Revised per Amendment 13)

Management of ARIA-H differed in 201 OLE compared to Study 301 because in 201 OLE dosing would continue for severe asymptomatic ARIA-H. In 301 Core, study drug would temporarily be stopped for > 10 cumulative ARIA-H and resumed, and permanently stopped if more ARIA-H was accrued. Approach to symptomatic ARIA-H was similar in 201 OLE and 301 Core.

Table 58 Management of ARIA-H in 201 OLE

Clinical Symptom Severity	ARIA-H Severity on MRI		
	Mild	Moderate	Severe
Asymptomatic	Continue dosing	Continue dosing	Continue dosing
Symptomatic	Temporarily stop dosing until ARIA-H is stabilized and subject is no longer symptomatic	Temporarily stop dosing until ARIA-H is stabilized and subject is no longer symptomatic	Temporarily stop dosing until ARIA-H is stabilized and subject is no longer symptomatic

In 201 OLE, similar to 301 Core resumption of treatment following symptomatic ARIA-H could only occur twice, after which the subject was discontinued from the study (Revised per Amendment 12).

Subjects who developed asymptomatic ARIA-H, could continue on the study and did not require additional MRI follow up outside the regularly scheduled assessment) with the following exceptions: subjects who developed multiple (> 10) asymptomatic cerebral microhemorrhages, superficial siderosis, or a single cerebral hemorrhage (greater than 10 mm at greatest diameter) could continue on the study uninterrupted per the Schedule of Assessments, with an unscheduled safety visit (with MRI) at approximately 30 days after the MRI features were first identified and further safety visits (with MRI) at approximately every 30 days until the asymptomatic ARIA-H stabilized radiographically.

Subjects who discontinued study treatment because of ARIA-E or ARIA-H, were to undergo the early termination visit within 7 days of discontinuation and undergo the 3 month Follow Up Visit per protocol. These subjects would continue to be followed with safety MRIs on a monthly basis thereafter, until the finding either resolved or stabilized.

12.1.9. ARIA and Cerebral Hemorrhage Tables and Selected Narratives Study 301

Table 59 Incidence of Treatment Emergent ARIA in New Exposures in 301 OLE

Preferred Terms	Lecanemab (N = 714)
Total Subjects with any Adverse Events	140 (19.6%)
ARIA-E	98 (13.7%)
Amyloid related imaging abnormality-edema/effusion	98 (13.7%)
ARIA-H	110 (15.4%)
Amyloid related imaging abnormality-microhemorrhages and hemosiderin deposits	99 (13.9%)
Superficial siderosis of central nervous system	40 (5.6%)

Safety population and TRTEMFL = Y
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Table 60 Incidence of Treatment Emergent ARIA on Lecanemab in 301 Core and OLE

Preferred Terms	Lecanemab (N =1612)

Preferred Terms	Lecanemab (N =1612)
Total Subjects with ARIA	365 (22.,6%)
ARIA-E	219 (13.6%)
Amyloid related imaging abnormality-oedema/effusion	219 (13.6%)
ARIA-H	298 (18.5%)
Amyloid related imaging abnormality-microhemorrhages and hemosiderin deposits	258 (16.0%)
Superficial siderosis of central nervous system	96 (6.0%)
Cerebral hemorrhage*	9 (0.6%)

Safety population and TRTEMFL = Y
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*Includes one cerebral hemorrhage event occurring within 40 days after last dose of study drug, added by the reviewer.

ARIA by ApoE genotype

Table 61 Treatment Emergent ARIA Summary by ApoE e4 Genotype in 301 Core

	Placebo N=897 N (%)			Lecanemab N=898 N (%)		
	Non-carrier N=286 N(%)	Heterozygote N=478 N(%)	Homozygote N=133 N(%)	Noncarriers N=278 N(%)	Heterozygote N=479 N(%)	Homozygote N=141 N(%)
ARIA	11 (4)	44(9)	29(22)	37(13)	91(19)	63(45)
SAES	1(0.3)	0	0	3(1)	3(0.6)	4(3)
Discontinuations	1(0.3)	1(0.2)	0	3(1)	8(2)	15(11)
Interruptions	2(0.7)	3(0.6)	4(3)	7(3)	33(7)	39(28)
Symptomatic ARIA	0	1(0.2)	1(0.8)	4(1)	12(3)	13(9.2)
ARIA-E	1(0.3)	9(2)	5(4)	15(5)	52(11)	46(33)
SAES	0	0	0	2(0.7)	2(0.4)	3(2)
Discontinuations	0	0	0	3(1)	2(0.4)	9(6)
Interruptions	0	3(0.6)	3(2)	7(2)	29(6)	34(24)
Symptomatic	0	0	0	4(1)	8(2)	13(9)
ARIA-H	11(4)	41(9)	28(21)	32(12)	66(14)	54(38)
SAES	0	0	0	1(0.4)	0	1(0.7)
Discontinuations	0	1(0.2)	0	2(0.7)	5(1)	10(7)
Interruptions	2(0.7)	2(0.4)	2(1.5)	3(1)	18(4)	20(14)
Symptomatic	0	1(0.2)	1(1)	2(0.7)	4(1)	5(4)
Cerebral hemorrhage* > 1 cm	0	0	0	1 (0.4)	3(0.6)	2(1.4)
SAES	0	0	0	1(0.4)	2(0.4)	1(0.4)
Discontinuations	0	0	0	0	1(0.2)	0
Interruptions	0		0	1(0.4)	3(0.4)	2(1)
Symptomatic	0	0	0	1(0.4)	2(0.4)	0

**Includes cerebral hemorrhage occurring within 40 days after last dose of study drug* (b) (6)

New exposures in 301 OLE (placebo in 301 Core)

The incidence of ARIA-E and ARIA-H remained highest in the ApoE e4 homozygotes in new exposures in 301 OLE (Table 62).

Table 62 Incidence of Treatment Emergent ARIA by APOE Genotype in New Exposures in 301 OLE

	Noncarriers N=218 n (%)	Heterozygotes N=388 n (%)	Homozygotes N=108 n (%)
ARIA or cerebral hemorrhage	21(10)	71(18)	49(45)
ARIA-E	13(6)	47(12)	38(35)
ARIA-H	17(8)	56(14)	37(34)
ARIA-H microhemorrhage	13(6)	51(13)	35(32)
Superficial Siderosis	6(3)	21(5)	13(12)
Cerebral Hemorrhage > 1 cm	1(1)	1(0.3)	1(1)

Safety population and TRTEMFL = Y
[taeariaapoe5.rtf] [taeariaapoe5.sas] 01MAY2023, 21:5

In the combined 301 Core and OLE, homozygotes for the ApoE ε4 allele had a higher risk of both ARIA-E and ARIA-H that were comparable to the homozygotes receiving lecanemab during the double-blind period of Study 301 Core. (Table 63).

Table 63 Incidence of Treatment Emergent ARIA by ApoE Status in 301 Core and OLE combined

	Non-Carrier	**Heterozygote**	**Homozygote**
	LEC10-BW (N=496) N (%)	**LEC10-BW (N=867) N (%)**	**LEC10-BW (N=249) N (%)**
ARIA or cerebral hemorrhage	71 (14.3)	178 (20.5)	119 (47.8)
ARIA-E	32 (6.5)	101 (11.6)	86 (34.5)
ARIA-H	59 (11.9)	140 (16.1)	99 (39.8)
ARIA-H microhemorrhage	42 (8.5)	125 (14.4)	91 (36.5)
Superficial Siderosis	22 (4.4)	43 (5.0)	31 (12.4)
Cerebral Hemorrhage > 1 cm	2 (0.4)	4* (0.3)	3 (1.2)

Safety population and TRTEMFL = Y
[taeariaapoe2.rtf] [taeariaapoe2.sas] 12APR2023, 12:2
**subject* (b) (6) *who had a nontreatment emergent ARIA-H event <40 days after last dose of study drug included.*
**subject* (b) (6) *who had a cerebral bleed 92 after last dose of study drug and subsequent to a brain biopsy not included*

Table 64 Incidence of Treatment Emergent ARIA in 201 OLE

Preferred Terms	Lecanemab (N = 180)
ARIA-E	15 (8.3%)
Amyloid related imaging abnormality-oedema/effusion	15 (8.3%)
ARIA-H	28 (15.6%)
Amyloid related imaging abnormality-microhemorrhages and hemosiderin deposits	24 (13.3%)
Superficial siderosis of central nervous system	8 (4.4%)
Cerebral hemorrhage	1 (0.6%)

Safety population and TRTEMFL = Y
[taearia2.rtf] [taearia2.sas] 03MAY2023, 21:14

In the 201 OLE study, 28 (16 %) of the subjects were homozygotes for the ε4 allele, 97 (54 %) were heterozygote, and 55 (31%) were noncarriers. ARIA-E was more commonly observed in carriers of the ApoE ε4 allele compared to noncarriers (observed in 14 % homozygotes, 10 % heterozygotes and 2 % in noncarriers

ARIA Radiographic Severity

Table 65 Incidence of Treatment Emergent ARIA by Maximum Radiologic Severity in Study 301 Core

Preferred Terms	Severity	Placebo (N = 897)	Lecanemab (N = 898)
ARIA-E	Missing	0 (0.0%)	1 (0.1%)
	Mild	9 (1.0%)	37 (4.1%)
	Moderate	6 (0.7%)	66 (7.3%)
	Severe	0 (0.0%)	9 (1.0%)
	Total	15 (1.7%)	113 (12.6%)
Amyloid related imaging abnormality-oedema/effusion	Missing	0 (0.0%)	1 (0.1%)
	Mild	9 (1.0%)	37 (4.1%)
	Moderate	6 (0.7%)	66 (7.3%)
	Severe	0 (0.0%)	9 (1.0%)
	Total	15 (1.7%)	113 (12.6%)
ARIA-H	Missing	0 (0.0%)	0 (0.0%)
	Mild	73 (8.1%)	97 (10.8%)
	Moderate	5 (0.6%)	24 (2.7%)
	Severe	2 (0.2%)	31 (3.5%)
	Total	80 (8.9%)	152 (16.9%)

Preferred Terms	Severity	Placebo (N = 897)	Lecanemab (N = 898)
Amyloid related imaging abnormality-microhemorrhages and hemosiderin deposits	Missing	0 (0.0%)	0 (0.0%)
	Mild	64 (7.1%)	79 (8.8%)
	Moderate	3 (0.3%)	19 (2.1%)
	Severe	1 (0.1%)	28 (3.1%)
	Total	68 (7.6%)	126 (14.0%)
Superficial siderosis of central nervous system	Missing	0 (0.0%)	0 (0.0%)
	Mild	17 (1.9%)	38 (4.2%)
	Moderate	2 (0.2%)	8 (0.9%)
	Severe	2 (0.2%)	4 (0.4%)
	Total	21 (2.3%)	50 (5.6%)
Cerebral hemorrhage*	Missing	0 (0.0%)	0 (0.0%)
	Mild	0 (0.0%)	2 (0.2%)
	Moderate	0 (0.0%)	2 (0.2%)
	Severe	0 (0.0%)	2 (0.2%)
	Total	0 (0.0%)	6 (0.7%)

Source: Clinical Analyst Created Table. Safety population and TRTEMFL = Y, [taeariasev1.rtf] [taeariasev1.sas] 12APR2023, 09:49
*One subject who had cerebral hemorrhage less than 40 days after last dose with severe radiological severity included

Table 66 Incidence of Treatment Emergent ARIA by Maximum Radiologic Severity in the Study 301 OLE

Preferred Terms	Severity	Lecanemab (N =1385)
ARIA-E	Missing	1 (0.1%)
	Mild	28 (2.0%)
	Moderate	65 (4.7%)
	Severe	16 (1.2%)
	Total	110 (7.9%)
Amyloid related imaging abnormality-oedema/effusion	Missing	1 (0.1%)
	Mild	28 (2.0%)
	Moderate	65 (4.7%)
	Severe	16 (1.2%)
	Total	110 (7.9%)
ARIA-H	Missing	1 (0.1%)
	Mild	107 (7.7%)
	Moderate	38 (2.7%)
	Severe	30 (2.2%)
	Total	176 (12.7%)
Amyloid related imaging abnormality-microhemorrhages and hemosiderin deposits	Missing	1 (0.1%)
	Mild	105 (7.6%)
	Moderate	28 (2.0%)
	Severe	25 (1.8%)
	Total	159 (11.5%)

Preferred Terms	Severity	Lecanemab (N =1385)
Superficial siderosis of central nervous system	Missing	0 (0.0%)
	Mild	27 (1.9%)
	Moderate	14 (1.0%)
	Severe	6 (0.4%)
	Total	47 (3.4%)
Cerebral hemorrhage	Missing	0 (0.0%)
	Mild	2 (0.1%)
	Moderate	0 (0.0%)
	Severe	1 (0.1%)
	Total	3 (0.2%)

Source: Clinical Analyst Created Table Safety population and TRTEMFL = Y.
[taeariasev4.rtf] [taeariasev4.sas] 27APR2023, 08:08, Clinical Analyst Created

Table 67 Incidence of Treatment Emergent ARIA by Maximum Radiologic Severity in the Study 301 Core + OLE

Preferred Terms	Severity	Lecanemab (N =1612)
ARIA-E	Missing	2 (0.1%)
	Mild	62 (3.8%)
	Moderate	130 (8.1%)
	Severe	25 (1.6%)
	Total	219 (13.6%)
Amyloid related imaging abnormality-oedema/effusion	Missing	2 (0.1%)
	Mild	62 (3.8%)
	Moderate	130 (8.1%)
	Severe	25 (1.6%)
	Total	219 (13.6%)
ARIA-H	Missing	1 (0.1%)
	Mild	186 (11.5%)
	Moderate	53 (3.3%)
	Severe	58 (3.6%)
	Total	298 (18.5%)
Amyloid related imaging abnormality-microhemorrhages and hemosiderin deposits	Missing	1 (0.1%)
	Mild	168 (10.4%)
	Moderate	39 (2.4%)
	Severe	50 (3.1%)
	Total	258 (16.0%)
Superficial siderosis of central nervous system	Missing	0 (0.0%)
	Mild	65 (4.0%)
	Moderate	21 (1.3%)
	Severe	10 (0.6%)
	Total	96 (6.0%)
Cerebral hemorrhage	Missing	0 (0.0%)

Preferred Terms	Severity	Lecanemab (N =1612)
	Mild	4 (0.2%)
	Moderate	2 (0.1%)
	Severe	3 (0.2%)
	Total	9 (0.6%)

Source: Extracted from Clinical Analyst created table. Safety population and TRTEMFL = Y, [taeariasev2.rtf] [taeariasev2.sas] 12APR2023, 09:49
One subject who had cerebral hemorrhage <40 days after last dose with severe radiological severity included

Table 68 Incidence of Treatment Emergent ARIA by Maximum Radiologic Severity in Study 201 OLE

Preferred Terms	Severity	Lecanemab (N = 180)
ARIA-E	Questionable Presence	0 (0.0%)
	Mild	4 (2.2%)
	Moderate	7 (3.9%)
	Severe	4 (2.2%)
	Total	15 (8.3%)
ARIA-H	Questionable Presence	20 (11.1%)
	Mild	6 (3.3%)
	Moderate	2 (1.1%)
	Severe	0 (0.0%)
	Total	28 (15.6%)
Amyloid related imaging abnormality-microhemorrhages and hemosiderin deposits	Questionable Presence	16 (8.9%)
	Mild	6 (3.3%)
	Moderate	2 (1.1%)
	Severe	0 (0.0%)
	Total	24 (13.3%)
Superficial siderosis of central nervous system	Questionable Presence	7 (3.9%)
	Mild	1 (0.6%)
	Moderate	0 (0.0%)
	Severe	0 (0.0%)
	Total	8 (4.4%)
Cerebral hemorrhage	Questionable Presence	0 (0.0%)
	Mild	1 (0.6%)
	Moderate	0 (0.0%)
	Severe	0 (0.0%)
	Total	1 (0.6%)

Source: Extracted from Clinical Analyst created table
Safety population and TRTEMFL = Y.[taeariasev2.rtf] [taeariasev2.sas] 18APR2023, 11:32

Table 69 Incidence of Treatment Emergent SAEs, Discontinuations, Interruptions and TEAEs Attributed to ARIA or Cerebral Hemorrhage in 301 Core

		Placebo N=897 n(%)	Lecanemab N=898 n (%)

ARIA Overall	SAES	0	7 (0.8)
	Discontinuations	1 (0.1)	25 (3)
	Interruptions	9(1)	79(9)
	TEAEs	84 (9)	191 (21.3)
	Symptomatic ARIA	2(0.2)	29 (3)
ARIA-E	SAES	0	7 (0.8)
	Discontinuations	0	14 (2)
	Interruptions	6(1)	70(8)
	TEAEs	15(1.7)	113 (13)
	Symptomatic ARIA-E	0	25(3)
ARIA-H microhemorrhage	SAES	0	2 (0.2)
	Discontinuations	1 (0.1)	15 (2)
	Interruptions	4(0.4)	36(4)
	TEAEs	68 (8)	126(14)
	Symptomatic ARIA-H	2(0.1)	9 (1)
ARIA-H superficial siderosis	SAES	0	0
	Discontinuations	0	4 (0.4)
	Interruptions	2(0.2)	13(1)
	TEAEs	21 (2)	50(6)
	Symptomatic superficial siderosis	0	2 (0.2)
Cerebral hemorrhage* > 1 cm	SAES	0	3(0.3%)
	Discontinuations	0	1(0.1)
	Interruptions	0	2(0.2)
	TEAEs	0	6(0.7)
	Symptomatic Cerebral Hemorrhage	0	3(0.3)

Source: Extracted From Clinical Analyst Created Tables adae.xpt
** includes cerebral hemorrhage > 1 cm occurring within 40 days of last dose*

Table 70 Incidence of Treatment Emergent SAEs, Discontinuations, Interruptions and TEAEs Attributed to ARIA and Cerebral Hemorrhage in 301 OLE

		N=1385 n (%)
ARIA	SAES	18(1)
	Discontinuations	24(2)
	Interruptions	87(6)
	TEAEs	209(15.1)
	Symptomatic	34(3)
ARIA-E	SAES	11(1)
	Discontinuations	16(1)
	Interruptions	74(5)
	TEAEs	110(8)
	Symptomatic	29(2)

ARA-H microhemorrhage	SAES	7(1)
	Discontinuations	11(1)
	Interruptions	45(3)
	TEAEs	159(12)
	Symptomatic	15(1)
ARIA-H superficial siderosis	SAES	2(0.1)
	Discontinuations	3(0.2)
	Interruptions	16(1)
	TEAEs	47(3)
	Symptomatic	4(3)
Cerebral Hemorrhage	SAES	3(0.2)
	Discontinuations	3(0.2)
	Interruptions	0
	TEAEs	3(0.2)
	Symptomatic	1(0.1)

Source: Extracted from Clinical Analyst Created Tables using adae.xpt

Table 71 Incidence of Treatment Emergent SAEs, Discontinuations and TEAEs Attributed to ARIA and Cerebral Hemorrhage in 301 Core and OLE Combined

		N=1612 n (%)
ARIA Overall	SAES	21 (1)
	Discontinuations	50 (3)
	Interruptions	162 (10)
	TEAEs	365 (22.6)
	Symptomatic	62 (3.8)
ARIA-E	SAES	18 (1.1)
	Discontinuations	31 (1.9)
	Interruptions	142 (9)
	TEAEs	219 (13.6)
	Symptomatic	54 (3.3)
ARA-H microhemorrhage	SAES	9 (0.6)
	Discontinuations	27 (1.7)
	Interruptions	79 (5)
	TEAEs	258 (16.0)
	Symptomatic	24 (1.5)
ARIA-H superficial siderosis	SAES	2(0.1)
	Discontinuations	7 (0.4)
	Interruptions	29(2)
	TEAEs	96 (6.0)
	Symptomatic	6 (0.4)
Cerebral Hemorrhage	SAES	7(0.4)
	Discontinuations	4(0.2%)
	Interruptions	4(0.2)

	TEAEs Symptomatic	9* (0.6) 4(0.2)

Source: Extracted from Clinical analyst created Tables
** includes cerebral hemorrhage occurring within 40 days of last dose.*

201 OLE

As of the 90-day updated 201 OLE CSR, there were only minor changes in the 201 OLE ARIA events compared to the previous review; there was one additional subject with ARIA-E and two additional subjects with ARIA-H (Table 70).

Table 72 Incidence of Treatment Emergent SAEs, Discontinuations and TEAEs Attributed to ARIA in 201 OLE

		N=180 n(%)
ARIA-E	SAES Discontinuations Interruptions TEAEs Symptomatic	1 (0.6) 0 8(4) 15 (8.3) 3(1,7)
ARA-H microhemorrhage	SAES Discontinuations Interruptions TEAEs Symptomatic	0 0 3(2) 24(13.3) 0
ARIA-H superficial siderosis	SAES Discontinuations Interruptions TEAEs Symptomatic	1 (0.6)) 0 3(2) 8 (4) 0
Cerebral Hemorrhage	SAES Discontinuations Interruptions TEAEs Symptomatic	1 (0.6)) 0 (0) 1(0.6) 1 (0.6)) 1(0.6)

Source: extracted from Clinical Analyst Crated Tables

Table 73 ARIA Symptom Resolution within the Period of Observation in 301 Core

	Number of Subjects with Symptomatic ARIA	Recovered/ Resolved	Resolved with Sequela	Recovering/ Resolving	Not recovered/ Not resolved

ARIA-E	25	23	1	0	1
ARIA-H overall	11	6	0	2	3
ARIA-H microhemorrhage	9	5	0	1	3
ARIA-H superficial siderosis	2	1	0	1	0

Source ADXA dataset. Clinical reviewer created
One subject had a seizure due to ARIA-E which was resolved, but the investigator identified this as resolved with sequela due to ongoing antiepileptic use. In one subject headaches occurring due to ARIA-E had not resolved at the time of study drug discontinuation. Three subjects who had symptomatic ARIA-H continued to have malaise, dizziness and gait disturbance, and headaches at the time of study discontinuations.

Timing of ARIA

Table 74 Timing of ARIA-E in 301 OLE

Number of Doses Prior to ARIA-E	N (n-110)	Cumulative Frequency N(%)
1	2	2 (2)
2	3	5 (5)
3	5	10 (9.5)
4	11	21 (19)
5	50	71(64.5)
6	5	76(69)
7	21	97(88)
8	1	98(89)
9	1	99(90)
11	5	104(94.5)
12	4	108((98)
13	1	109(99)
24	1	110 (110)

Sources: adae.xpt, reviewer created

Table 75 Timing of First ARIA-E in 201 OLE

	Lecanemab (N = 15)	
Numbers of Dose Prior ARIA-E	N	Range of Days from Last Dose to First ARIA-E
4	2	9- 12
5	1	8- 8
6	5	1- 32
7	1	12- 12
12	1	19- 19
13	1	22- 22
16	1	14- 14
22	1	2- 2
24	1	78- 78
51	1	2- 2

Numbers of Dose Prior ARIA-E	Lecanemab (N = 15) N	Range of Days from Last Dose to First ARIA-E

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Radiographic Duration of ARIA-E

In 301 Core, the first ARIA-E event in those on LEC10-BW resolved by the 12th week in 52% (59 out of 113), by 17 weeks in 81% (91 out of 113), and in all subjects eventually during the course of the study. Of all the ARIA-E events (n=172) occurring in 113 subjects on LEC10-BW, 52% (89 out of 172) of ARIA-E events resolved by 12 weeks, and 80% (137 out of 192) of ARIA-E events by 17 weeks, and 99 % overall. In one subject, who had a second ARIA-E event after the last dose of study drug in 301 Core ((b) (6) there was no resolution of ARIA-E during the follow up period.

Table 76 Duration (days) of First Episode of Treatment-Emergent Radiographic ARIA in 301 Core

Statistics	Placebo (N = 15)	Lecanemab (N = 113)
N	13	113
Mean	72.69	91.67
SD	50.76	57.56
Median	67.00	90.00
Min	25.0	16.0
Max	188.0	374.0
95% CI	42.0-103.4	80.9-102.4

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Radiographical duration of ARIA-E in subjects who were new exposures in 301 OLE (placebo in Core), was on average 89 days (SD 50, range 22-308 days). ARIA-E resolved at about 13 weeks in 45% (43 out of 96) subjects who are new exposures and experienced a first ARIA-E event in the 301 OLE, and in 60% (58 out of 96) at 17 weeks, and over 17 weeks in 17 subjects.

Table 77 Duration (days) and Outcome of First Episode of Treatment-Emergent Radiographic ARIA in 301 Core and OLE Combined.

Statistics	Lecanemab 10mg/bi-weekly (N = 219)
N	197
Mean	88.77
SD	54.29

Statistics	Lecanemab 10mg/bi-weekly (N = 219)
Median	85.00
Min	16.0
Max	374.0
95% CI	81.1- 96.4

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Antithrombotic use and ARIA

Table 78 Incidence of ARIA-H and Cerebral Hemorrhage on Lecanemab with Anti-Thrombotic Use Preceding ARIA -H in 301 Core and OLE Combined

	ARIA-H n(%)	Cerebral Hemorrhage* n(%)
Not on an antithrombotic anytime	183 / 991 (19)	4 / 991 (0.4)
On anti-thrombotic prior to ARIA-H	105 / 573 (18)	5 / 573 (1)
Aspirin ≤81 mg alone	55 / 268 (21)	0 / 268
Aspirin>81 mg, other antiplatelet or combination of aspirin (any dose) with another antiplatelet	30 / 206 (15)	1 / 206 (1)
Anticoagulation (alone or combined with antiplatelet or aspirin)	21 / 147 (14)	4 / 147 (3)

Represents events of ARIA-H or cerebral hemorrhage that occurred between the time when the incident ARIA-H or cerebral hemorrhage was observed and the previous MRI when it was not observed; the denominator is the total number of individuals on a selected antithrombotic category during that window.
ARIA-H includes microhemorrhages and superficial siderosis
S*ource: May 1, 2023, Applicant response to information request (Table sBLA IR9-2mod) (modified to exclude subjects*
**Modified to include cerebral hemorrhage occurring within 40 days of last dose of study drug (excludes subject (b) (6) who was not on an antithrombotic, and had cerebral hemorrhage 90 days after last dose of study drug).*
Anticoagulation also includes one subject who received tissue plasminogen activator.

301 Core ARIA narratives

Deaths

There were no ARIA related deaths in 301 Core. In 301 OLE there were 3 deaths ((b) (6) (b) (6) and (b) (6) that were possibly related to ARIA or cerebral hemorrhage. See Section 7.4.1 for a detailed narrative of these subjects.

SAEs

ARIA

Below I summarize illustrative SAEs of ARIA-E, ARIA-H, and cerebral hemorrhage occurring in the lecanemab trials.

ARIA-E

The following table summarizes SAEs of ARIA in 301 Core and OLE. Narratives of selected SAEs are included below.

Table 79 Serious Symptomatic ARIA Events in 301 Core and OLE

Subject ID **Age, sex** **ApoE genotype**	**# of doses taken ****	**ARIA-E Radiographic Severity/Serious**	**ARIA-H (Co-Occurring or Isolated) Radiographic Severity/Serious**	Symptoms/Treatment	**Clinical Severity**	Outcome of Clinical Event
(b) (6) 80-year-old female E3/E3 Core	3rd	Moderate/ Serious	10 microhemorrhage Severe/Serious	Headache, left arm weakness, high blood pressure/Dexamethasone	Moderate	Resolved
(b) (6) 67-year-old male E4/E4 Core	4th	Moderate/ Serious	39 microhemorrhage Severe/Not Serious	Acute confusion, memory loss/dexamethasone	Moderate	Resolved
(b) (6) 80-year-old female E3/E4 Core	5th	Severe/ Serious	11 microhemorrhage; Co-occurring subdural hematoma Severe/Not Serious	Aphasia, /	Severe	Resolved
(b) (6) 78-year-old male E3/E3 Core	1st	Moderate/ Serious	No	Confusion	Moderate	Resolved
(b) (6) 88-yearold male E4/E4 Core	3rd	Severe/ Serious	92 Microhemorrhage, superficial siderosis Severe/Not Serious	Seizure, cortical blindness, apraxia/ Levetiracetam	Severe	Resolved
(b) (6) 68-year-old female E3/E4 Core	1	Unknown	2 new microhemorrhages	Seizure, hemianopsia aphasia, confusion; Lacosamide Clonazepam	Severe	Resolved
(b) (6) 69-year-old female E3/E4 OLE	5	Severe/Not serious	81 ARIA-H microhemorrhages Severe/Serious	Gait disturbances, possibly seizure leading to fall/cervical fracture/ confusion, and disorientation Levetiracetam Decadron	Severe	Not recovered/not resolved
(b) (6) 80-year-old-female E3/E4 OLE	3	Severe/ Serious	2 microhemorrhages Mild/ Serious	Headache, disorientation seizure), hypertensive emergency, intermittent visual scintillations, left gaze preference Levetiracetam dexamethasone	Severe	Unknown
(b) (6) 80-year-old male E3/E4 OLE	7 & 8 (continued dosing	Severe/ Serious	Mild/nonserious	Confusion, dysphasia Seizure EEG epileptic activity Diazepam	Severe	Recovered /Resolved

	after original ARIA-E)			Valproic Acid methylprednisolone		
(b) (6) 62-year-old-male E4/E4 OLE	3	Severe/ Serious	Not in Extension OLE	left hemiparesis and left homonymous lateral hemianopia, worsening cognitive function None	Severe	Recovering/Resolving
(b) (6) 59-year-old female E3/E3 OLE	3	Moderate/ Serious	Severe ARIA-H	hemianopia homonymous, impaired reasoning and bradyphrenia dexamethasone	Severe	Not Recovered/Not Resolved
(b) (6) 74-year-old female y/o male E4/E4 OLE	41	Severe/ Serious	53 new microhemorrhages severe	General discomfort, seizure, drowsy Methylprednisolone	Moderate	Recovered/Resolved
(b) (6) 68-yearo-old male E4/E4 OLE	3	Severe/ Serious	Severe/Serious > 10 Microhemorrhage Superficial Siderosis	Headache, homonym hemianopsia, , dyscognitive seizures, visual perseveration, visual hallucinations, gait impairment	Severe	Recovered/Resolved
(b) (6) 65-year-old-male E4/E4 OLE	3	Moderate/ Serious	Severe/ Serious	Mild Headache, confusion , aphasia Lorazepam Dexamethasone Levetiracetam	Severe	Recovered/Resolved
(b) (6) 70-year-old female E3/E4 OLE	2	Severe/ Serious	4 areas of Superficial siderosis Severe/Serious	Seizures, headache, delirium, dizziness, decline in subject's athletic ability, and worsening cognitive function Lorazepam, dexamethasone, levetiracetam, etomidate	Severe	Not recovered/resolved

**LEC10BW in Core all others in 301 ole are new exposures to study drug*
***this reflects the number of lecanemab doses*
The following subjects had a serious ARIA event that was asymptomatic: in 301 Core (b) (6) *) and 301 OLE* (b) (6)) *. In these cases the serious designation was made because the event was a medically important event. These subjects are not included in the table above.*
In subjects (b) (6) according to the database (ADXA), per sponsor symptoms of symptomatic ARIA resolved. This reviewer, based on the narratives, adjudicated (b) (6) to be resolved with sequela and (b) (6) to not be resolved.

Selected illustrative narratives below demonstrate the morbidity associated with serious ARIA-E highlight the variety of symptoms of symptomatic ARIA-E, and the impact this has on individual patients.

(b) (6)

68-year-old female who was ApoE e4 heterozygous had been on rivaroxaban, and had no microhemorrhages on screening MRI. On study day 148 she received the 11th dose of study drug. On study day 156, she experienced difficulty walking and upon arrival at the emergency room she had a convulsive seizure followed by postictal neurologic defects lateralized

hemianopsia, aphasia and confusion. She had a second generalized tonic clonic seizure, before she could recover from the first episode. MRI showed vasogenic edema, in the left parieto-occipital temporal and right occipital temporal regions without enhancing lesions, few micro bleeds and hypersignal in the pulvinar nuclei. She was hospitalized for severe and serious symptomatic ARIA-E. Rivaroxaban was stopped and she was switched to apixaban. She was treated with lacosamide and clonazepam. EEG showed metabolic encephalopathy. Study drug was permanently discontinued due to severe ARIA-E. On study day 159, she was diagnosed with acute pulmonary edema, with oxygen saturation in the 85 % and echocardiogram revealed left ventricular dysfunction. She was transferred to the ICU where she received non-invasive ventilation and was treated with diuretics and antibiotics. She also was found to have transitionary atrial fibrillation. She was started on methylprednisolone. She also sustained a T12 fracture. She had significant back pain, and required assistance for walking, and had radiographical evidence of myelopathy at T12 level. On study day 181 she had exacerbation of confusional state. Oxycodone was discontinued and lacosamide reduced. On study day 186 she sustained a fall, and due to difficulty with resumption of walking was transferred to a rehabilitation center.

On study day 223, a repeat MRI showed significant global brain atrophy as compared to the last MRI assessed before the onset of ARIA-E. On study day 225, the subject was neurologically stable except for some degree of cognitive decline following 2 months of in-hospital care, and gait instability secondary to T12 fracture. No further seizures were observed. On study day 250, she underwent elective laminectomy for T11-T12. On study day 229, it was reported that the vertebral fracture resolved with sequela of radicular pain and gait instability. Seizures and thoracic vertebral fracture were considered as ARIA-E associated clinical symptoms. On study day 488, 341 days after the last dose of study drug she experienced ARIA-H, with 2 new microhemorrhages in the left parietal regions. On study day 498, the subject was discontinued from the Core study due to ARIA-E.

Reviewer Case: While this subject's ARIA-E event resolved, she ended up having a prolonged and complicated hospital stay due to complications of severe, serious symptomatic ARIA-E. Additionally, she sustained sequela of gait impairment and cognitive decline and her brain MRI at follow up suggested significant global atrophy compared to last MRI prior to ARIA-E. Another observation noted in this narrative is that this subject had significant atrophy noted on MRI over a course of 4 months with coincident worsening cognition. It is possible that prolonged hospitalization in a patient with Alzheimer's disease may have contributed to cognitive decline observed in this patient.

(b) (6)

68-year-old male who was ApoE e4 homozygous and at screening had 2 microhemorrhages in the left frontal, and one in the right parietal lobes. He received the third dose of study drug on study day 29. On study day 35, he had a radiographically severe ARIA-E in the right and left frontal, right and left temporal (nonhippocampal) right and left parietal, and right and left occipital regions. He was symptomatic with blurry vision which was mild in severity. On study

day 47, he was found to have 27 new microhemorrhages for a total of 29 microhemorrhages, deemed to be asymptomatic. On study day 52 he presented to the emergency room with convulsions and was hospitalized. He also was observed to have a focal seizure with secondary generalization. His exam showed cortical blindness and apraxia. During the hospital stay he was treated with levetiracetam. He experienced tonic clonic seizures which resolved on study day 54. Study drug was interrupted with the last dose given on study day 29. On study day 54, after remaining seizure free and with improvements in the cortical blindness he was discharged from the hospital upon his family's request. On study day 58 MRI sowed two new microhemorrhages for a total of 31 microhemorrhages. On study day 76, there was improvement on the ARIA-E. On study day 104, ARIA-E had decreased and was limited to the occipital lobes. On the same Day he had 61 new microhemorrhages for a total of 92 microhemorrhages. These were reported to be asymptomatic. On study day 104, he also had an ARIA-H superficial siderosis in the left frontal lobe. On study day 122, he had three new ARIA-Microhemorrhages in the left temporal cortical level. On study day 152 ARIA-E had decreased further, and on study day 229 ARIA-E had resolved. A total of 92 microhemorrhages were reported on study day 352. Subject discontinued from the 301 Core due to ARIA-E.

Reviewer Comment: This narrative describes an ApoE e4 homozygote who had symptomatic ARIA-E with seizures, apraxia and cortical blindness after the third dose of study drug. In this case, the subject continued to accumulate a large number of microhemorrhages, cumulatively 92, while the ARIA-E was still radiographically present, but radiographically improving.

Narratives of patients with serious ARIA in 301 Core and OLE (not all symptomatic)

(b) (6)

80-year-old female who was not a carrier of the ApoE ε4 allele, was not on antithrombotic per narrative, and did not have any microhemorrhages on screening MRI, received the 3rd dose of study drug on study day 32. On study day 36, she experienced "mini-strokes", as she was acting different than usual, and her daughter also noted that something was wrong with her smile. She had a headache. She took a fall in her house without any injuries and was noted to have left arm weakness, along with headache and high blood pressure. She was hospitalized on study day 39 and on exam she had left pronator drift, orbiting around left arm, slightly weakness in the right arm and leg. On study day 39, an MRI revealed she had radiographically moderate ARIA-E in the left frontal region which was deemed to be serious. On the same day she had ARIA-H with 10 new microhemorrhages in the right frontal aera. The ARIA-E was deemed to be serious and symptomatic. On study day 4, she had mild left hemiparesis and decreased attention. She was treated with dexamethasone 2mg po bid which was gradually reduced. On study day 41, her MMSE improved from 27 to 30, and her exam was almost normal with the exception of mild drift in the left arm. The study drug was permanently discontinued due to serious ARIA-E and ARIA-H.

(b) (6)

67-year-old male who was an ApoE e4 homozygote. At screening he had one cerebellar microhemorrhage. He was not on an antiplatelet or anticoagulation per narrative. He received the 4th dose of study drug on study day 43. On study day 44, he sustained a radiographically moderate ARIA-E in the left frontal and left occipital region. On study day 72, he experienced ARIA-H microhemorrhage with 15 new microhemorrhages in the left frontal region and there was an increase in the size of the original ARIA-E. On study day 84, he presented to the emergency room after experiencing acute confusion and amnesia, and olfactory changes. He was treated with dexamethasone 8mg IV TID, lacosamide, and levetiracetam for seizure prophylaxis. The sponsor did not consider this event as treatment emergent as study drug was last administered on study day 43. On study day 103, 24 new microhemorrhages were reported totaling 39 microhemorrhages. On study day 159 he was discontinued from Study 301 core.

Reviewer Comment: This subject had worsening of a treatment emergent ARIA-E event observed 29 days after last dose of study dug, followed by new neurological symptoms occurring 12 days after worsening of the ARIA-E (41 days after the last dose of study drug), suggesting that the PD effects of study drug may continue beyond 30 days.

(b) (6)

80-year-old female who was ApoE e4 heterozygote had no microhemorrhages at screening. The subject received the 5th dose of study drug on study day 50. On study day 72, she developed aphasia and had difficulty following instructions. She was hospitalized for further work up. CSF studies were normal. MRI on study day 73 showed radiographically severe ARIA-E. Same day she was also found to have 11 new microhemorrhages. The study drug was permanently discontinued for serious symptomatic ARIA-E. On study day 82, symptomatic right cerebral ARIA-E improved from moderate to mild in severity. On study day 109 a second event of ARIA-E was identified in the right occipital region. A maximum of 11 new microhemorrhages were identified as well as a subdural hematoma was identified.

Reviewer Comment: This subject with one ApoE e4 allele sustained severe ARIA-E after the 5th dose of study drug which was symptomatic. This subject also had a subdural hematoma associated with the ARIA-E and ARIA-H microhemorrhages which has been observed to occur with ARIA in lecanemab treated subjects.

<u>301 OLE</u>

(b) (6)

80-year-old female who was ApoE e4 heterozygous, received placebo during the 301 Core study. She received the first dose of study drug on extension day 1, and the same day she complained of intermittent headaches. She received the 3rd dose of study drug on extension day 22. On extension day 30 she again complained to her family of headaches, and on study day

31 she was evaluated by a nurse, who sent er to the ER. In the ER she was noted to have a left sided gaze deviation, blood in the mouth, weakness. It was though that she likely had a seizure prior to hospitalization. On extension day 32, CT scan showed edema in the right temporal occipital lobe and left posterior temporal lobe consistent with vasogenic rather than cytotoxic edema. She was diagnosed with ARIA-E on this day. It was classified as severe, symptomatic and serious. She was treated with levetiracetam 500mg iv, and dexamethasone. On extension day 32, she was also found to have a hypertensive urgency. On extension day 59, ARIA-H with 2 microhemorrhages was reported. This was also classified as symptomatic, severe in clinical severity and serious. The study drug was permanently discontinued due to the events of ARIA-E and ARIA-H. She was discharged from the hospital on an unknown date. She discontinued from the extension OLE on extension day 64, and outcome of adverse event was listed as recovering, resolving.

Reviewer Comment: This narrative illustrates that a new complaint of headache in patients early during treatment with lecanemab may be a symptom underlying ARIA-E, and that providers should have a low threshold for obtaining and unscheduled MRI especially in ApoE ε4 carriers.

(b) (6)

74-year-old male who was ApoE e4 homozygote, received lecanemab during 301 Core. He completed the Core study and entered 301 OLE. At screening he had no evidence of ARIA, microhemorrhage, macrohemorrhage or superficial siderosis on MRI. He received the last dose of Study Drug on study day 534 and entered 301 OLE. He received the third dose of study drug on extension day 28. On extension day 39, he experienced generalized discomfort., and following this had two generalized tonic-clonic seizures on extension day 41. He was admitted to the hospital and found to be drowsy. CSF studies was done which only showed mild hypoproteinemia. On study day 42, MRI brain showed radiographically severe ARIA-E located in the right frontal, right and left temporal, right and left parietal, right and left occipital areas. ARIA-E was classified clinically as moderate and serious. There also was ARIA-H microhemorrhage consisting of 53 new microhemorrhages in the left parietal (4), right temporal (12), left occipital (12), right occipital (15), right parietal (5), and right frontal (5). ARIA-H was reported as asymptomatic, mild in clinical severity and nonserious. Due to persistence of drowsiness methylprednisolone treatment was initiated. He recovered from generalized tonic clonic seizures on extension day 41. The study drug was permanently discontinued due to ARIA-E. The subject was discharged from the hospital on extension day 48 and was recovering from the drowsiness with ARIA-E and ARIA-H ongoing at the time of the study cutoff period.

Reviewer Comment: This is a very unusual case as the subject, who is a homozygote for the ApoE ε4 allele, completed the 301 Core study on lecanemab, with no reported ARIA-E and had ARIA-E after the third dose in the 301 OLE. This presentation is more consistent with newly exposed ε4 homozygotes, who have ARIA-E early in the course of the treatment. There was only a gap of 15 days between the last dose of study drug in the 301 Core and 301 OLE.

(b) (6)

79-year-old female who was ApoE e4 heterozygous, received placebo during the 301 Core. On study day 529 she had ARIA-H superficial siderosis (20mm in the right parietal area), which was asymptomatic. She received the 2nd dose of study drug on extension day 15. On extension day 26 she complained of a headache. She woke up on extension day 27, and while watching television she experienced a seizure that lasted for one minute with her eyes and head turned to the left and altered mental status. She was unable to communicate. Shortly after she had another seizure lasting for 2 minutes with left hand tremor, drooling and cyanosis. She was transferred via ambulance to the hospital. She had a third episode of seizure lasting 2-3 minutes, with closed eyes, and let hand tremor in the ambulance. Upon arrival to the emergency room, she was observed to have a left gaze preference, and left arm weakness (Todd's paralysis). She was diagnosed with severe and serious ARIA-E which was symptomatic with seizures. CTA ruled out a stroke and showed multifocal low attenuating lesions in the bilateral parietooccipital and temporal lobes. Edema in bilateral temporal lobes was reported. Her gaze preference improved after administration of lorazepam. She was treated with dexamethasone, levetiracetam and etomidate as well as iv fluids. EEG could not be performed due to severe agitation. CSF study did not show any infections. She was given quetiapine and lorazepam for delirium. On extension day 28, MRI showed multifocal T2/Flair high signal intensity with cortical swelling in the bilateral parieto-occipital and temporal lobes. There was either superficial siderosis or subarachnoid hemorrhage in the right parietal sulcus and microbleeds in the right temporal lobe. The MRI suggested PRES, ARIA-E and ARIA-H. ARIA-E and ARIA-H were categorized as severe, symptomatic, and serious. She continued to have delirium during the course of her hospital stay, and PI considered co-morbid Lewy Body Dementia due to parkinsonism (although she was also receiving treatment with quetiapine). She was started on memantine, and rivastigmine was increased, and she was discharged on study day 39 from the hospital. On study day 58 a follow up MRI revealed radiographically severe ARIA-E in the right frontal/temporal, right parietal, right occipital, left frontal, left temporal, left parietal and left occipital areas. It was severe and serious. New ARIA-H superficial siderosis was reported for a total of 4 regions: left occipital (20mm), right parietal (30mm, still present and increased in size), 3 right occipital (10-mm). ARIA-H was reported as severe in clinical severity, asymptomatic and serious. On study day 67, the subject visited the site for assessment and reported ongoing dizziness and headaches. She also had decline in her athletic ability and worsening of the cognitive function. Study Drug was discontinued on extension day 15, and her status was described as recovering.

Reviewer Comment: This is a description of a patient who carried one ApoE e4 allele, and had fulminant ARIA, with cognitive and physical sequela ongoing at the time of study drug discontinuation.

Narratives of Subjects who had mild symptomatic ARIA-E and were continued dosing

(b) (6)

63-year-old ApoE e4 heterozygous male who after the 6th dose of study drug was diagnosed with radiographically mild symptomatic ARIA-E, with moderately severe headaches and study drug was continued with no adverse events and subject completed 301 Core and joined extension.

(b) (6)

73-year-old female, who was not a carrier of the ApoE e4 allele, and had a relevant past medical history of hyperlipidemia, bundle branch block left arrhythmia, ventricular extrasystole, supraventricular tachycardia, type 2 diabetes mellitus supraventricular extrasystole, received the 12th dose of study drug on study day 174. On the same day she was found to have mild ARIA-E in the left occipital region and was symptomatic with moderate headache. No action was taken with study drug and ARIA-E resolved on study day 224. She received the last dose of study drug on study day 359, and study drug was ultimately permanently discontinued after she had a pacemaker which unqualified her for study participation. Forty-seven days after the last dose of study drug, the subject experienced syncope. The subject discontinued from 301 Core on study day 645.

(b) (6)

64-year-old female who was ApoE e4 homozygous, completed 301 Core on placebo, received the 7th dose of study drug on extension day 78. On the same day a radiographically mild ARIA-E was identified. Symptoms of agitation were reported. Both ARIA-E and agitation were reported to be resolve on extension day 141. Dosing continued for mild symptomatic ARIA-E without interruption. She received the 10th dose on extension day 196 and her participation in the 301 OLE was ongoing at the time of the data cutoff of December 1, 2022.

Cerebral Hemorrhage

Table 80 Subjects with Cerebral Hemorrhage On Lecanemab

SUBJID Age, sex Apo E status	# of microhemorrhages prior to first dose of lecanemab	# of doses prior to event/days since last dose	Concurrent ARIA-E, ARIA-H or other AE of interest	Serious Severity	Clinical Symptoms	Anticoagulation or Thrombolytic	Outcome
301 Core							
(b) (6) 75-year-old female E4/E4	0	4 doses 1 day	Radiographically moderate ARIA-E (colocalized with cerebral hemorrhage) Subdural hemorrhage	Serious Moderate	None	Yes Ticagrelor	Study drug discontinued
(b) (6) 78-year-old male E4/E4	0	13 doses 10 days	ARIA-H superficial siderosis (colocalized with cerebral hemorrhage)	Not Serious Mild	None	Yes Warfarin Baby Aspirin	Study drug interrupted, then restarted, completed Core, ongoing in OLE

							N/A
(b) (6) 69-year-old male E3/E4	0	30 doses 7 days	No	Serious Severe	Left sided weakness, asthenia slurring words	None	Study Drug Discontinued Symptoms Not recovered, not resolved
(b) (6) 65-year-old male E3/E4	0	12 doses 9 days	ARIA-H microhemorrhage (co-localized)	Not Serious Mild	None	None	Study drug interrupted then restarted, completed Core, ongoing in OLE
(b) (6) 70-year-old female E3/E4	3	4 doses 40 days	ARIA-E (co-localized), ARIA-H microhemorrhage On day of 4th dose, then worsening in ARIA-E and ARIA-H 30 days later Also subarachnoid hemorrhage	Serious Severe	Sudden frontal headache, secondary generalization of simple focal visual and motor seizure, partial hemianopsia, spatial neglect, monoparesis	Yes rivaroxaban	Study Drug Discontinued Initial symptoms resolved but had sequela of difficulty handling problems, daily tasks, unable to function independently after the cerebral hemorrhage
(b) (6) 79-year-old female E3/E3	0	26 doses 5 days	None	Serious Moderate	Abnormal behavior and speech disorder,	No	Initial symptoms resolved but had sequela from cerebral hemorrhage necessitating staying in private residential home
301 OLE							
(b) (6) 71-year-old female E3/E4	0	27 doses 91 days	ARIA-H microhemorrhage Superficial siderosis, left parietal space occupying lesion (all in left parietal area) 6 days after biopsy cerebral hemorrhage and subdural hemorrhage	Nonserious Mild	Asymptomatic	No	Discontinued due to glioblastoma
(b) (6) 80-year-old female E3/E4	0	5 doses 2 days	ARIA-H microhemorrhage Superficial Siderosis Severe ARIA-E (co-localized)	Serious Mild	Asymptomatic	Yes Apixaban	Study drug permanently discontinued N/A
(b) (6) 85-year-old male E3/E3	3 (possibly more?)	9 doses 19 days	ARIA-H microhemorrhage ARIA-E (co-localized)	Serious Mild	Confusion	Yes Apixaban and aspirin	Fatal
(b) (6) 63-year-old, female E4/E4	0	3 doses 5 days	Unknown	Serious Severe	Garbled speech	Yes Tissue plasminogen activator	Fatal
201 Core + OLE							

(b) (6) 77-year-old male E3/E3	3	12th dose 0 days	ARIA-H microhemorrhage	Not Serious Mild	Asymptomatic	325 mg aspirin and history of thrombocyt openia	Study drug discontinued
(b) (6) 68-year-old female E3/E3	0	3rd dose 7 days		Serious Severe	Intermittent headache, loss of vision in right field	81 mg of ASA	Study drug interrupted then restarted; dosing ongoing
101							
(b) (6) 81-year-old male ApoE genotype unknown	0	First dose 20 days	none	Not serious Mild n	Asymptomatic	None	Resolved No action taken (single dose per study)

- The column " outcome" was based on information provided in the narrative, and did not always align with the variable "outcome of clinical event" in the ADXA dataset (for example for subject (b) (6) in the ADXA dataset, outcome of clinical events of headache, monoparesis and partial seizure were recovered/resolved, however after this hospitalization, subject had decline in daily functioning. Similarly for subject (b) (6) while the symptoms of behavior disorder and speech disorder resolved according to the ADXA dataset, this subject also had a decline in functioning, necessitating staying in a residential care center).

As of December 1, 2022, in 301 Core of the 6 cerebral hemorrhages on lecanemab occurring within 40 days of the last dose of study drug, 4 were serious ((b) (6)). ApoE e4 carriership was homozygote in one (b) (6)), heterozygote in two ((b) (6)) subjects and one subject (b) (6) was a noncarrier. Of these only (b) (6) was noted to have three microhemorrhages at screening MRI (suggesting possible cerebral amyloid angiopathy). In subjects (b) (6) , and (b) (6) cerebral hemorrhage occurred in the setting of ongoing ARIA-E and ARIA-H microhemorrhage. While in subject (b) (6) , the cerebral hemorrhage occurred 40 days after the study drug administration, ARIA-E had radiographically worsened one day prior to the diagnosis of the cerebral hemorrhage. In both of these cases the cerebral hemorrhage (including the nontreatment emergent event) was likely related to study drug. Subject (b) (6) had been on ticagrelor for stent placement, and subject (b) (6) was on rivaroxaban for history of pulmonary embolism. In subjects (b) (6) isolated cerebral hemorrhage occurred on study day 441, 6 days after the subject received the last dose of study drug. Subject (b) (6) also experienced an isolated cerebral hemorrhage which occurred 4 days (on study day 439) after the last dose of study drug was administered on study day 434. Neither subject (b) (6) nor (b) (6) was on an antithrombotic. Three subjects were symptomatic: Subject (b) (6) had slurred speech and left sided weakness, subject (b) (6) had abnormal behavior and speech disorder, and subject (b) (6) presented with secondary generalization of a simple focal visual and motor seizures, and headache. He was also found to have a left lateral homonymous hemianopsia, spatial neglect. At the end of the hospitalization this subject was having impaired reading capacity, difficulty in handling problems and daily tasks, impairment of patient's function at home and unable to function independently regarding shopping and transports. Subject had worsening of dysexecutive syndrome, severe impairment of working memory and topographic disorientation.

Outcome of clinical symptoms was not recovered/not resolved for (b) (6) (with ongoing symptoms of dysarthria and asthenia). While the initial symptoms of ARIA-H were recovered / resolved in subjects (b) (6) and (b) (6) based on the ADXA dataset, both of these subjects were described in the narrative to have had a decline in their functional status after these events, thus the symptoms resolved but both patients had sequela from symptomatic cerebral hemorrhage.

As of December 1, 2022, of the 3 cerebral hemorrhages occurring within 40 days of the last dose of study drug, all three (b) (6)) were serious, and two were symptomatic and fatal ((b) (6),o) Subject (b) (6) similar to subjects (b) (6) and (b) (6), was a carrier of the ε 4 allele, was a new exposure to study drug (received placebo during 301 Core) and after the 4th dose of study drug experienced radiographically severe ARIA-E, cerebral hemorrhage as well as ARIA-H microhemorrhage and superficial siderosis. She was on apixaban which was discontinued after the cerebral hemorrhage, and the study drug was permanently discontinued. She remained asymptomatic, and she is ongoing in the extension study, with all ARIA-H events ongoing at the time of the data cut off. See Section 7.4.1 Deaths for narratives of subjects (b) (6) and (b) (6)

Additionally, there was one additional serious TEAE of thalamus hemorrhage during the 301 OLE. Subject (b) (6), who was an ApoE ε4 homozygote sustained a thalamic hemorrhage on extension day 276 during her participation in the 301 OLE. During the 301 Core this subject received placebo but sustained 6 new microhemorrhages. After the 7th dose of lecanemab on extension day 78 she sustained two new microhemorrhages for a total of 8 microhemorrhages. She also sustained mild ARIA-E in the left frontal region which increased from radiographic severity of mild to moderate on extension day 106. On this day she also had one more microhemorrhage for a total of 9 microhemorrhages. Study drug was interrupted until extension day 169. She had an adverse event of ARIA-H superficial siderosis on in the left frontal region on extension day 134. She remained asymptomatic. On study day 169, the subject sustained a fall from her bicycle after alcohol intake and was briefly hospitalized for clavicle fracture and nausea/vomiting. Study drug was restarted on extension day 218 . She received the 13th dose of study drug on study day 260. Sixteen days later, on extension day 276 she was hospitalized with a symptomatic left thalamus hemorrhage and study drug was discontinued. She was treated with nicardipine, lansoprazole and amlodipine. Her symptoms were right hemiplegia, severe somatic hypoesthesia, aphasia, lack of insight into the disease and disorder of generalized attention. On extension day 309 she recovered from the acute phase of thalamic bleed and was recovering. This subject had a history of hypertension and excessive alcohol consumption and hepatic cirrhosis. In her case, it is not clear if the thalamic hemorrhage is related to study drug, given other risk factors including hypertension, alcohol use and cirrhosis.

Reviewer Comment: Subjects (b) (6) (all carriers of the ε4 allele) all *experienced a cerebral hemorrhage co-occurring with ARIA-E, with or without ARIA-H microhemorrhage and superficial siderosis. Two were on an anticoagulant and one on an*

antiplatelet. I can't rule out the possibility that mechanisms that lead to ARIA while on lecanemab treatment increases the risk of cerebral hemorrhage, which may be further increased if also taking concomitant anticoagulation or antiplatelet medications. Subjects (b) (6) *and* (b) (6) *were reported to have cerebral hemorrhage on lecanemab treatment associated with a fatal outcome. Both had received placebo during the 301 Core and were new exposures to study drug in the OLE. Subject* (b) (6) *had complained of a headache starting after the first dose of lecanemab, and had focal neurological symptoms after the 4th dose of study drug, and received tPA for a presumed stroke, and had catastrophic widespread bleeding that led to death. It is unknow whether she had ARIA-E as the cause of her focal neurological symptoms leading to presumed stroke diagnosis. In this case, it is again possible that mechanisms that lead to amyloid removal and ARIA, increase the risk of bleeding which was further aggravated by use of tPA. In the case of subject* (b) (6)*, the presentation was more complicated as the patient had been on anticoagulation for atrial fibrillation and had sustained a couple of falls prior to the cerebral hemorrhage. In the case of* (b) (6)*, there is also the possibility of underlying cerebral amyloid angiopathy.*

Two subjects ((b) (6) *) had isolated cerebral hemorrhage after the last dose of study drug without any occurrence of ARIA prior. None had microhemorrhages at screening to suggest underlying cerebral amyloid angiopathy. In these instances, I am unable to conclusively determine if the cerebral hemorrhage was related to study drug.*

Narratives of Cerebral Hemorrhages:

301 Core:

(b) (6)

75-year-old female who is ApoE ε4 homozygous, and at the time of the screening MRI did not have any microhemorrhages, superficial siderosis or ARIA. She had an event of coronary artery disease on study day -51 at which time she underwent stent placement and was started on ticagrelor. She received the 4th dose of study drug on study day 48. On the same day her MRI showed radiographically moderate ARIA-E in the left frontal, right temporal, right and left occipital regions. On the same day she had a cerebral hemorrhage that was 30 mm in size in the right occipital region and a subdural hematoma in the right frontal area. The study drug was interrupted due to ARIA-E and cerebral hemorrhage. The investigator and neurologist felt that macrohemorrhage and subdural hematoma were related to stent placement and concomitant medication of ticagrelor and were not typical of monoclonal antibody side effects. On study day 48 she was sent to the ER for further evaluation. She was admitted for monitoring, and a CT in the hospital showed the bleed to be stable with some mass effect in the occipital lobe of the right lateral ventricle. There was a 2mm midline shift due to the subdural hematoma. She was started on levetiracetam for seizure prophylaxis. The study drug was temporarily interrupted due to cerebral hemorrhage ARIA-E and ARIA-H. Concomitant treatment with ticagrelor was discontinued. She received dexamethasone for the ARIA-E. She remained asymptomatic through this event. She was discharged from the hospital on study day

52. On study day 135 she sustained an ARIA-H with 2 microhemorrhage and a 12 mm superficial siderosis in the let frontal region (these were not considered treatment emergent as the study drug was last administered on study day 48). The subject was discontinued from study drug and study participation per patient's withdrawal.

Reviewer Comment: Both the cerebral hemorrhage and subdural hemorrhage were related to study drug as they occurred in the setting of ARIA-E, after the 4th dose of the study drug. Subdural hematoma has been observed before in the setting of ARIA-E in other subjects treated with lecanemab. It is possible that ticagrelor may have increased her risk of bleeding further while on treatment with lecanemab. The microhemorrhages and superficial siderosis on study day 135 occurred 87 days after the last dose of study drug, and 29 days after the ARIA-E had resolved radiographically, therefore relationship to study drug is not known. I cannot rule out that this subject also has underlying cerebral amyloid angiopathy.

(b) (6)

This is a 69-year-old male who was ApoE ε4 heterozygous, who at baseline had no microhemorrhages, superficial siderosis or ARIA. On study day 321, he was briefly hospitalized for an event of angina pectoris, which resolved the same day. He was not reported to be on an antithrombotic. He received the last dose of study drug on study day 435. On study day 441, the patient was noted to be slurring his words and having left sided weakness. He was taken to the hospital and hospitalized for a cerebral hemorrhage. CT showed a 59cc acute parenchymal hematoma in the right cerebral hemisphere. Repeat CT on study day 442 showed increased size and increased mass effect and shift. On study day 44 he underwent right sided craniotomy. The study drug was permanently discontinued due to the event of cerebral hemorrhage with the last dose taken on study day 435. He was discharged to a nursing home. The event of cerebral hemorrhage was ongoing at the time of study discontinuation.

(b) (6)

79-year-old ApoE ε4 allele noncarrier, who on screening MRI did not have any microhemorrhages, superficial siderosis or ARIA. She received the 26th dose of study drug on study day 435. On study day 439 this subject experienced a cerebral hemorrhage, which was moderate in severity, serious, and symptomatic with abnormal behavior and speech disorder. She was hospitalized and study drug was temporarily interrupted and never restarted. On study day 536 she was discharged with a diagnosis of left parietal subcortical cerebral hemorrhage with edema measuring 3.4cm x 2.4 cm in the surrounding area. She had not been on an antithrombotic prior to this event.

(b) (6)

This is a 70-year-old female who was ApoE ε4 heterozygote who had been on rivaroxaban, was noted to have three microhemorrhages at her screening MRI. On study day 46, the subject received the 4th dose of study drug. On study day 50, the subject experienced radiographically moderate ARIA-E in the right parietal, right occipital and left occipital lobes. She remained asymptomatic. On the same day she sustained 3 new microhemorrhages (in the right frontal

and right occipital areas), for a total of 6 microhemorrhages. She remained asymptomatic. Study Drug was temporarily stopped due to ARIA-E and ARIA-H. On study day 80 follow up MRI showed increased size in ARIA-E, and the same day, there were 2 new microhemorrhages noted for a total of 8 microhemorrhages. On study day 85 the subject experienced a brief simple focal visual and motor seizure with intact awareness followed by secondary tonic-clonic generalized seizure with post ictal mild transitory monoparesis of the left arm. She also complained of a headache. CT obtained showed a right occipital subarachnoid hemorrhage superposed on preexisting vasogenic edema, and in the right and let occipital and right parietal areas. She also had a 32 mm right occipital intracerebral lobar hemorrhage. Rivaroxaban was interrupted and anticoagulation was reversed. The subject was hospitalized with left lateral homonymous hemianopsia and mild to moderate headache. On study day 106, MRI revealed stability of findings. On study day 106, she also had partial homonymous hemianopsia and subarachnoid hemorrhage, and spatial neglect which had improved partially. Around study day 228, the subject had impaired reading capacity, difficulty in handling problems and daily tasks, impairment of patient's function at home and unable to function independently regarding shopping and transports. Subject had worsening of dysexecutive syndrome, severe impairment of working memory and topographic disorientation. As of study day 228, the event of symptomatic ARIA-H (right parietal macrohemorrhage) was recovering.

(b) (6)

78-year-old ApoE ε4 homozygous male, who had no baseline microhemorrhages at screening MRI and was not on an antithrombotic. He received the 13th dose of study drug on study day 166. On study day 175, radiographically moderate ARIA-E was identified in the right frontal, temporal areas. On the same day a 10 mm superficial siderosis as well as a cerebral hemorrhage (32mm) were both noted in the right temporal, nonhippocampal area. Study Drug was interrupted, and he remained asymptomatic. Study Drug was restarted on study day 287, after decline in size of the cerebral hemorrhage. The subject continued with study participation in the 301 Core and entered the OLE. He remained asymptomatic.

(b) (6)

This is a 65-year-old ApoE ε heterozygote who had no microhemorrhages at screening and was not on an antithrombotic. He received the 12th dose of study drug on study day 165. On study day 173, he had a new ARIA-H microhemorrhage in the right occipital region, as well as a 11 mm cerebral hemorrhage also in the same region. He remained asymptomatic. Study drug was temporarily interrupted and restarted on study day 213. ARIA-H was ongoing at the time of 301 Core completion. He entered the OLE phase and participation is ongoing.

301 OLE

(b) (6)

80-year-old ApoE ε4 heterozygote who received placebo during participation in 301 Core. She was on apixaban during the time she entered the OLE study. She received the 5th dose of study drug on study day 57. On extension day 58 she experienced a radiographically severe ARIA-E

event in the right and left temporal right and left parietal, right and left occipital regions, cerebral hemorrhage measuring 15mm in the right temporal region, ARIA-H with 2 new microhemorrhages, and three events of superficial siderosis (20mm in the left frontal, 15 mm in the right parietal region and a 30mm in the right occipital region). She remained asymptomatic. She was hospitalized and apixaban was discontinued. On extension day 73, cerebral hemorrhage reduced to 12 mm, and the superficial siderosis in the right parietal region increased to 50 mm. She also had two new superficial siderosis, a 20mm lesion in the left parietal region and a 15 mm lesion in the right frontal region. On extension day 85, the cerebral hemorrhage increased to 16 mm, and the superficial siderosis increased in size as well. On the same day she also had a new microhemorrhage. ARIA-E remained radiographically severe. On study day 114, the ARIA-E improved to radiographically moderate, cerebral hemorrhage had decreased in size to 11 mm and the superficial siderosis increased to 45 mm in size in the right occipital region. On extension day 114, she had 4 new ARIA-H microhemorrhages. On extension day 143 the cerebral hemorrhage was resolved. On study day 170, ARIA-E improved to radiographically mild, and one new microhemorrhage was reported. On extension day 198 ARIA-E was resolved. As of the data cutoff of April 15, the subject was ongoing in the study.

(b) (6)
72-year-old female who is ApoE ε4 homozygote, received placebo during 301 Core. Based on information in the ADAE dataset this subject experienced ARIA-H microhemorrhage and ARIA-E during the 301 Core study. She received the first dose of study drug on extension day 1. During the 301 OLE she sustained a fall from a bike and had injuries with confusion and clavicle fracture. It was noted that the fall from the bicycle was due to use of alcohol. On extension day 276 she sustained a left thalamic bleed. Her records are silent to ARIA-E or ARIA-H during the 301 OLE study. She did have a history of hypertension which may have contributed to the thalamic hemorrhage. She was treated with nicardipine, lansoprazole and amlodipine. During hospitalization she was also found to have takotsubo cardiomyopathy requiring urgent catheterization performed, and also had a urinary tract infection. Due to hepatic cirrhosis and tendency toward low blood pressure, some of her blood pressure medications were discontinued upon transfer to the hospital. She was discontinued from study due to multiple complications and was reported to be recovering from the bleed.

Narratives for subjects (b) (6) who died during the 301 OLE period due to cerebral hemorrhage can be found in Section 7.4.1 Deaths.

Cerebral hemorrhage in placebo

Subject (b) (6) who is a 76-year-old ApoE4 heterozygous had cerebral hemorrhage while on placebo during 301 Core. This narrative is provided as an example that in this study population spontaneous events of ARIA and cerebral hemorrhage, while rare may occur. This subject was not on any antithrombotics. On study day 170 after the 13th dose of placebo, this subject had a left cerebellar infarction, On study day 180, they had an ARIA-H superficial siderosis. On study

day 180, the subject had ARIA-E involving the right temporal, parietal and occipital regions identified by study MRI. The ARIA-E was mild but progressed to a maximum radiographic severity of moderate on study day 239. Study drug was interrupted at this time, with the last dose taken on study day 239. A second event of ARIA-H superficial siderosis occurred on this day. On study day 329 the subject experiencing tingling, burning and numbness in both arms. The subject was unable to sleep and was restless. CT showed acute parenchymal hemorrhage of 3.2x2.8x2.6 cm as well as subarachnoid hemorrhage. He was discharged from the hospital. During the follow up period she sustained a second event of cerebral hemorrhage in the right temporal region as well as a superficial siderosis. The second event of cerebral hemorrhage also was symptomatic with drooling, dysphagia, and gait disturbance. This was ongoing at the time of discontinuation.

Table 81. Incidence of Treatment Emergent ARIA Related Symptoms in Study 301 Core

Preferred Terms	Placebo (N = 897)	Lecanemab (N = 898)
Subjects with ARIA Related Symptoms	2 (0.2%)	31 (3.5%)
ARIA-E related symptoms	0 (0.0%)	25 (2.8%)
Amnesia	0 (0.0%)	1 (0.1%)
Aphasia	0 (0.0%)	1 (0.1%)
Ataxia	0 (0.0%)	1 (0.1%)
Cognitive disorder	0 (0.0%)	1 (0.1%)
Confusional state	0 (0.0%)	4 (0.4%)
Diplopia	0 (0.0%)	1 (0.1%)
Dizziness	0 (0.0%)	3 (0.3%)
Fall	0 (0.0%)	1 (0.1%)
Fatigue	0 (0.0%)	1 (0.1%)
Generalized tonic-clonic seizure	0 (0.0%)	1 (0.1%)
Glare	0 (0.0%)	1 (0.1%)
Hallucination	0 (0.0%)	1 (0.1%)
Headache	0 (0.0%)	12 (1.3%)
Hyporesponsive to stimuli	0 (0.0%)	1 (0.1%)
Muscular weakness	0 (0.0%)	1 (0.1%)
Nausea	0 (0.0%)	3 (0.3%)
Paresthesia	0 (0.0%)	1 (0.1%)

Preferred Terms	Placebo (N = 897)	Lecanemab (N = 898)
Partial seizures with secondary generalization	0 (0.0%)	1 (0.1%)
Tinnitus	0 (0.0%)	1 (0.1%)
Vision blurred	0 (0.0%)	1 (0.1%)
Visual acuity reduced	0 (0.0%)	1 (0.1%)
Visual impairment	0 (0.0%)	1 (0.1%)
Vomiting	0 (0.0%)	1 (0.1%)
ARIA-H related symptoms	2 (0.2%)	11 (1.2%)
Confusional state	0 (0.0%)	2 (0.2%)
Dizziness	1 (0.1%)	3 (0.3%)
Gait disturbance	0 (0.0%)	1 (0.1%)
Headache	0 (0.0%)	4 (0.4%)
Malaise	0 (0.0%)	1 (0.1%)
Migraine	1 (0.1%)	0 (0.0%)
Muscular weakness	0 (0.0%)	1 (0.1%)
Retinal hemorrhage	0 (0.0%)	1 (0.1%)
Visual impairment	0 (0.0%)	1 (0.1%)
Macrohemorrhage related symptoms	0 (0.0%)	2 (0.2%)
Asthenia	0 (0.0%)	1 (0.1%)
Behavior disorder	0 (0.0%)	1 (0.1%)
Dysarthria	0 (0.0%)	1 (0.1%)
Speech disorder	0 (0.0%)	1 (0.1%)

Safety population and TRTEMFL = Y
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Table 82 Incidence of Treatment Emergent ARIA-Related Symptoms in 301 Core and OLE Combined

Preferred Terms	Lecanemab (N =1612)
Subjects with ARIA Related Symptoms	65 (4.0%)
ARIA-E related symptoms	54 (3.3%)
Agitation	1 (0.1%)

Preferred Terms	Lecanemab (N =1612)
Amnesia	1 (0.1%)
Anxiety	1 (0.1%)
Aphasia	3 (0.2%)
Ataxia	1 (0.1%)
Blood pressure increased	1 (0.1%)
Bradyphrenia	1 (0.1%)
Cerebral disorder	1 (0.1%)
Cognitive disorder	1 (0.1%)
Confusional state	12 (0.7%)
Diplopia	1 (0.1%)
Disorientation	1 (0.1%)
Dizziness	3 (0.2%)
Electroencephalogram abnormal	1 (0.1%)
Fall	1 (0.1%)
Fatigue	2 (0.1%)
Focal dyscognitive seizures	1 (0.1%)
Gait disturbance	1 (0.1%)
Generalized tonic-clonic seizure	2 (0.1%)
Glare	1 (0.1%)
Hallucination	1 (0.1%)
Hallucination, visual	1 (0.1%)
Headache	26 (1.6%)
Hemianopia homonymous	2 (0.1%)
Hemiparesis	1 (0.1%)
Hypoesthesia	1 (0.1%)
Hyporesponsive to stimuli	1 (0.1%)
Impaired reasoning	1 (0.1%)
Lethargy	1 (0.1%)
Meniscus injury	1 (0.1%)

Preferred Terms	Lecanemab (N =1612)
Muscular weakness	2 (0.1%)
Nausea	3 (0.2%)
Paresthesia	1 (0.1%)
Partial seizures with secondary generalization	1 (0.1%)
Quadrantanopia	1 (0.1%)
Seizure	2 (0.1%)
Skin abrasion	1 (0.1%)
Thinking abnormal	1 (0.1%)
Tinnitus	1 (0.1%)
Vision blurred	1 (0.1%)
Visual acuity reduced	1 (0.1%)
Visual impairment	2 (0.1%)
Visual perseveration	1 (0.1%)
Visuospatial deficit	1 (0.1%)
Vomiting	1 (0.1%)
ARIA-H related symptoms	27 (1.7%)
Aphasia	1 (0.1%)
Confusional state	7 (0.4%)
Dizziness	4 (0.2%)
Gait disturbance	1 (0.1%)
Headache	11 (0.7%)
Hypersensitivity	1 (0.1%)
Lethargy	1 (0.1%)
Malaise	1 (0.1%)
Memory impairment	1 (0.1%)
Muscular weakness	1 (0.1%)
Photopsia	1 (0.1%)
Resting tremor	1 (0.1%)
Retinal hemorrhage	1 (0.1%)
Seizure	1 (0.1%)

Preferred Terms	Lecanemab (N =1612)
Superficial siderosis of central nervous system	1 (0.1%)
Visual impairment	1 (0.1%)
Macrohemorrhage related symptoms	4 (0.2%)
Aphasia	1 (0.1%)
Asthenia	1 (0.1%)
Attention deficit hyperactivity disorder	1 (0.1%)
Behavior disorder	1 (0.1%)
Confusional state	1 (0.1%)
Dysarthria	1 (0.1%)
Hemiplegia	1 (0.1%)
Hypoesthesia	1 (0.1%)
Nausea	1 (0.1%)
Pyrexia	1 (0.1%)
Speech disorder	1 (0.1%)

Safety population and TRTEMFL = Y
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Multiple ARIA-E Events

In Study 301 Core, twenty-eight subjects had more than 1 ARIA-E event, of whom 4 had more than 2 ARIA-E events. Of the four subjects who had more than 2 ARIA-E events, two were ApoE ε4 homozygotes (b) (6)) and two were heterozygote (b) (6)). Of the original ARIA-E events, worst clinical severity was mild in 23 and moderate in 5 ((b) (6) . Radiographic severity was mild in 4, moderate in 4 and severe in 2 (b) (6)). The occurrence of multiple events was not predictive of whether the event would be serious: in four subjects (b) (6)) the first ARIA-E event was symptomatic, in 7 subjects (b) (6)) the second ARIA-E event was symptomatic, and in one subject the third ARIA-E event was symptomatic ((b) (6)).

Of the 28 subjects with multiple ARIA-E events, maximum radiographic severity in the repeat ARIA-E events was mild in 2 subjects, moderate in 21 subjects, and severe in 5 subjects ((b) (6)). Of the 5 subjects with a radiographically severe repeat ARIA-E, 2 were symptomatic, one with moderate clinical symptoms (b) (6)) and one with mild clinical symptoms (b) (6)). See narratives below.

The experience with multiple episodes of ARIA is too limited to make generalizations about risk factors for multiple events, seriousness or severity of events, or about outcomes.

Some of the subjects who had multiple ARIA-E events on lecanemab during the 301 Core continued to have ARIA-E events during the OLE (such as subject (b) (6) described below). See selected representative narratives for subjects with multiple ARIA-E events below.

301 Core

(b) (6)

This is a 61-year-old APOE ε4 homozygote, who received the second dose of lecanemab in 301 Core on study day 20. On study day 22 the subject complained of a headache. On study day 28, she received the 3rd dose of lecanemab. On study day 32 MRI showed radiographically severe ARIA-E event, which was symptomatic. Clinical symptoms of headache were categorized as moderate in severity. Subject was treated with paracetamol and dexamethasone and lecanemab was interrupted. On study day 35 she also experienced ARIA-H for a total of 3 microhemorrhages (had two at baseline). On study day 51 she had 2 new microhemorrhages for a total of 5. She continued to sustain new macrohemorrhages and on study day 79 she had cumulatively 8 new microhemorrhages. Lecanemab was restarted on study day 146 after resolution of ARIA-E. She received a dose of lecanemab on study day 162. On study day 167 the subject reported headache, tinnitus, nausea and vomiting and was treated with dexamethasone, caffeine, codeine and paracetamol. ARIA-E was radiographically severe, and clinical symptoms were moderate. Lecanemab was interrupted, and on study day 235 ARIA-E resolved. Lecanemab was permanently discontinued on study day 162 for two episodes of severe symptomatic ARIA-E. She continued to sustain new macrohemorrhages with cumulatively 10 ARIA-H microhemorrhages on study day 226. According to the narrative the subject had no adverse events ongoing at the time of Core Study discontinuation.

(b) (6)

78-year-old female who was ApoE ε4 homozygote received the 3rd dose of study drug on study day 29. She had radiographically moderate ARIA-E which led to drug interruption until resolution of ARIA-E. On study day 155 lecanemab was resumed. She received the 15th dose of study drug on study day 323. On study day 330 she complained of mild intermittent headache. On study day 337 she received the 16th dose of study drug and also an MRI, which showed radiographically severe ARIA-E and 5 new ARIA-H microhemorrhages. The start date for ARIA was presumed to be study day 330 when she complained of headaches. study drug was interrupted with last dose taken on study day 337. On study day 368 she had a second episode of ARIA-H with 6 new microhemorrhages. On study day 399 she had a third episode of ARIA-H with 7 new microhemorrhages. Study drug was interrupted and restarted on study day 520. She completed 301 Core and entered the OLE study and her participation was ongoing.

70-year-old ApoE ε4 heterozygote who received the 13th dose of lecanemab on study day 170. On study day 177, he was found to have radiographically mild ARIA-E, which resolved on Study day 204. On study day 225 he received the 17th dose of lecanemab and on study day 253 he had a second episode of a radiographically mild ARIA-E. On Study day 254, he received the 19th dose of lecanemab. On study day 263 he had an episode of ARIA-H with four microhemorrhages. He received the 24th dose of lecanemab on study day 323. He developed symptoms of dizziness on study day 326. On study day 333, he was diagnosed with a third episode of radiographically mild ARIA-E. Lecanemab was interrupted and restarted on study day 352. The third episode of ARIA-E resolved on study day 354. He received the 27th dose of study drug of study day 379. He had a second episode of ARIA-H with one new microhemorrhage in the left frontal region. No treatment was reported with study drug. On study day 435 he received the 30th dose of lecanemab on study day 435, and on study day 438 had a fourth episode of radiographically mild ARIA-E. No action was taken with study drug, and the ARIA-E event resolved on study day 465. He had the last dose of study drug on study day 534 and completed Core as planned on study day 547 and entered the OLE.

He received the 12th dose (49th dose overall) of study drug on extension day 169. On extension day 168 he experienced increased confusion and marked worsening of memory. MRI showed one new microhemorrhage that was deemed to be symptomatic. As of data cut off of December 1, 2022, his participation was ongoing.

Selected narratives for subjects with multiple ARIA-E events in 301 OLE

(b) (6)

A 69-year-old female who is ApoE ε4 homozygous received the 9th dose of lecanemab on study day 168. On study day 178 she sustained one new ARIA-H microhemorrhage. She received the 21st dose of lecanemab on study day 343. On study day 371 she had radiographically moderate ARIA-E, which was asymptomatic. On this day she was also noted to have three new microhemorrhages for a total of 4 new microhemorrhages. Lecanemab was interrupted due to radiographically moderate ARIA-E until, resolution. On study day 428 lecanemab was restarted. She completed study 301 Core as planned and entered the OLE. On extension day 48 she received the 5th dose in the OLE (overall 34th dose of lecanemab). On the same day she was noted to have 3 new microhemorrhages for a total of 7 microhemorrhages, as well as radiographically mild ARIA-E which was symptomatic. No action was taken with lecanemab. On extension day 230, she received the 18th dose in OLE (47th dose overall) of lecanemab. On extension day 230 she had 7 new ARIA-H microhemorrhages for a total of 14. Lecanemab was interrupted due to this event until extension day 279 at which time it was restarted. Her participation in the 301 OLE was ongoing.

Reviewer Comment: This subject who sustained multiple ARIA events during treatment with lecanemab without any serious associated symptoms, demonstrates that in some individuals

multiple ARIA events may remain asymptomatic and not have any overt cognitive or other adverse outcomes.

(b) (6)

This is a 65-year-old ApoE ε4 homozygous male who completed 301 Core on placebo. He received the 4th dose of lecanemab on extension day 36, and had a radiographically moderate ARIA-E. On extension day 52, ARIA-H microhemorrhage with 6 new microhemorrhages for a total of 8 microhemorrhages were reported. Lecanemab was interrupted due to these events. On extension day 107, 71 days after the last dose of lecanemab, the subject had one new microhemorrhage for a total of 9. On extension day 135, 99 days after the last dose of lecanemab, he had four new microhemorrhage for a cumulative 13 microhemorrhages. Lecanemab was restarted on extension day 205. On extension day 266, the subject became confused, and could not communicate. Local MRI showed clinically severe ARIA-E and more than 10 ARIA-H (radiographically severe). On extension day 268 he was discharged from the stroke unit. On extension day 286, he had another episode of confusion and aphasia and was hospitalized. In the ER he was noted to be slightly confused with a speech impairment. CT angiogram was unchanged from his recent hospitalization. On an unknown date he was discharged from the hospital. There were no further details provided in the narrative. Subject was discontinued from study treatment due to ARIA-H and ARIA-H on study day 262.

Reviewer Comment: This subject who sustained multiple ARIA events during treatment with lecanemab demonstrates that some individuals with multiple ARIA events may have serious symptomatic ARIA-E with potential sequela.

12.1.10. Infusion Related Reactions and Hypersensitivity Reaction Tables and Selected Narratives in Study 301

Table 83 Treatment Emergent SAEs of Infusion Related Reactions and Hypersensitivity Reactions in Study 301 Core and OLE

	# of doses /Symptoms/Grade/Severity	Intervention/Outcome/Comments
301 Core		
(b) (6) IRR	30th dose, Increased confusion, generalized weakness, feeling "crummy" Grade 2 IRR/moderate severity	Hospitalized, work up revealed elevated BO and HR of 109. Given atorvastatin and baby aspirin. No action taken with study drug; IRR resolved same day. No recurrence of IRR with continued dosing.
(b) (6) IRR	1st dose Severe headache after infusion, mental status change Grade 2/ severe	Hospitalized, work up revealed urinary tract infection, and dehydration. No action taken with study drug. And patient completed 301 Core without premedication in subsequent doses.

(b) (6) IRR	26th dose, Vertigo the day after the infusion. Grade 2/moderate	Hospitalized, symptoms improved with meclizine, and Epley maneuver, also had syncope during bowel movement. Completed 301 Core dosing without premedication and no other episodes of IRR.
(b) (6) IRR	1st infusion Cyanosis, rigors, fever Grade 3/severe	Hospitalized and treated with iv fluids, diphenhydramine, famotidine, glucose, ondansetron, and paracetamol. Study drug discontinued.
(b) (6) IRR	1st infusion Chills, achiness, acute respiratory failure, hypoxia Grade 3, severe	Hospitalized and treated with diphenhydramine, oxygen, antibiotics, furosemide. Study drug discontinuation
(b) (6) IRR	1st infusion Chills, dyspnea with increased respiratory rate and retractions, basal wheezing. Back stiffness, CO_2 accumulation; nausea, vomiting Grade 4, severe (anaphylactoid reaction)	Hospitalized and treated with diphenhydramine, oxygen, epinephrine, Study drug discontinuation
(b) (6) IRR	1st infusion Muscle spasms, shivering, fever, nausea vomiting, lower back pain and diarrhea Grade 3/moderate	Hospitalized, treated with dexamethasone, paracetamol. Study Drug discontinued
(b) (6) IRR	1st Cold sensation, headache, hypertensive urgency, and syncope Grade 3 / severe	Hospitalization; treatment with furosemide, alprazolam Study drug discontinuation
(b) (6) IRR	1st infusion Shivering, hypertensive crisis, vomiting Grade 3 /severe	Hospitalized and treated with chlorphenamine, clonidine, furosemide, hydrocortisone, paracetamol. study drug discontinuation
(b) (6) IRR	1st infusion Fever, low blood pressure, erythematous plaques on legs, upper limbs and back waist	Mild. Hospitalization. Bile duct stone 3 days later. Study drug discontinued.
(b) (6) IRR	1st infusion Grade 2/mild Myalgias, chills, fever.	Hospitalization and treatment with nonsteroidal anti-inflammatory; Continued treatment in 301 Core and in 301 OLE.
(b) (6) Hypersensitivity reaction	1st infusion Moderate Nausea and fever	Hospitalized, found to have elevated WBC count, procalcitonin and C-reactive protein, started on antibiotics, blood, urine culture and x-ray negative. Study drug discontinued for hypersensitivity reaction.
301 OLE		
(b) (6)	36th dose Grade 2 / Moderate Chills, fevers and had confusion trouble breathing, and was not making sense.	Hospitalized for infusion related reaction versus infectious encephalopathy. Treated with amoxicillin and guaifenesin, and her mental status returned to baseline. Work up revealed left basilar pneumonia possibly due to aspiration. Study drug permanently Discontinued
(b) (6)	1st dose in OLE Grade 2 / moderate Chills, shortness of breath (O_2 saturation 80%.), nausea, shaking, low blood pressure	Hospitalized, and treated with paracetamol, azithromycin, ceftriaxone, and saline. Symptoms resolved the next day. Study drug permanently discontinued.
(b) (6)	1st infusion Grade 2 / moderate light-headed, chills, nausea, vomiting. hypotension	Taken to the ER treated with diphenhydramine, iv saline, ondansetron. Study drug permanently discontinued
(b) (6)	1st infusion Grade 3/moderate Chills, shaking, and low-grade fever	Diphenhydramine treatment at clinic, went home but woke up still confused with chills and difficulty moving. Was hospitalized on day 2 and symptoms improved with iv hydration ,

		Study drug permanently discontinued
(b) (6)	1st infusion Grade 3 / severe Tachycardia, diaphoresis, hypertension, tremors	Treated with diphenhydramine and paracetamol, after continued tachycardia, hospitalized, symptoms resolved 2 days later. Study drug was permanently discontinued.
(b) (6) IRR	1st infusion (premedicated with diphenhydramine) chills, rigors, neck, and back pain Grade 3 / moderate 9thnd infusion (premedicated with diphenhydramine Grade 1 / mild	Treated with paracetamol, hydrocortisone, 3 days later still with mild fever and malaise/headache, given ibuprofen and methylprednisolone. On extension day 4 had low lymphocyte count. Symptoms resolved by Day 8. Continued with study drug with premedication, had one other Serious IRR, after Low grade fever, treated with paracetamol and iv diphenhydramine
(b) (6) IRR	1st dose Chills, pyrexia Grade 2 / severe	Treated with dexamethasone, epinephrine, observed in the ER, resolved same day. Continued dosing participation ongoing.
(b) (6) Hypersensitivity	1st dose Left sided pleural chest pain after infusion	Started rivaroxaban for suspected PE, possible hypersensitivity rule out infection, started on doxycycline. Participation ongoing
(b) (6) IRR	1st dos Grade 2 / moderate Cold shivering, tachycardia, atrial fibrillation on ECG, perianal itching.	Dexamethasone, oxygen , transferred to ER, and discharged same day. Remained tired for a few days by 8 days resolved. Participation in the 301 OLE is ongoing.
(b) (6)	1st dose Grade 2 / Moderate Feeling cold, shivering and flushing to the chest	Treated with oxygen, paracetamol and hydrocortisone. Study drug permanently discontinued.
(b) (6)	1st dose Grade 1 / severe Chills, eructation, fever, headache, low blood pressure, nausea.	Hospitalization, supportive care, by next day improved. Study drug permanently discontinued
(b) (6)	1st dose Grade 2 / severe Chills, pyrexia,	Observed in the Emergency room, given dexamethasone, sodium chloride, epinephrine, oxygen. Received 27 doses of lecanemab and participation is ongoing.

IRR: Infusion related reaction
** The number of doses refers to the lecanemab doses (excluding placebo exposure)*
***All subjects in the 301 OLE with serious IRR or hypersensitivity, except* (b) (6)*, were new exposures and the SAE of IRR or hypersensitivity occurred after the first infusion.*

Grading of Infusion Reactions

The applicant used the NCI-CTCAE, Version 4.0, grading of allergic/hypersensitivity reactions/cytokine release, as follows (revised per Amendment 06): See Section 12.1.15 for CTCAE grading and management guidelines for infusion related reactions.

Majority of subjects in the 301 Core study had a Grade 2 infusion related reaction (Table 84)

Table 84 Maximum Toxicity Grading of Infusion Related Reactions in 301 Core

Standard Toxicity Grade	Placebo N=897	10 mg/kg bi-Weekly N=898
Grade 1	41 (7.4)	78(8.7)
Grade 2	25 (2.8)	149(16.6)
Grade 3	0	6(0.7)
Grade 4	0	1(0.1)

Reviewer created using the ADAE dataset, selected SAFFL=Y, TRTEMFL =Y,: Open Label Extension Flag=no, dictionary derived term= infusion related reactions. The highest toxicity rating for each individual was selected. This dataset then was grouped by dictionary derived term, USUBJID, and actual treatment for period 01 and tabulated by actual treatment for period 01 and toxicity grade.

Of the 7 subjects who reported Grade 3 ((b) (6) or Grade 4 ((b) (6) infusion related reaction, 5 (b) (6) were serious events and summarized in Table 80 Subjects who had a Grade 3 or 4 infusion related reaction reported increased blood pressure, heart rate and respiratory rate, rigors, chills, fevers and cyanosis (b) (6) respiratory failure and hypoxia with pulmonary edema (b) (6), whole body cold sensation, headache, syncope (b) (6)), nausea, vomiting, elevated blood pressure, heart rate, chills, and fever (b) (6) shivers, vomiting and , blood pressure of 190/90 mm Hg ((b) (6)

301 Core and OLE combined

Based on the data cut off of December 1, 2022, the incidence of infusion related reactions in combined 301 Core and OLE was 24% (395/1612). In the 301 Core and OLE combined of the 395 infusion related reactions 66% (259/1612) was mild, 31% (122/1612) was moderate and 4% (14/1612) was severe. 5% (20 out 395) were serious events.

In this combined dataset, 93% (366/395) of the subjects had at least one infusion after the first treatment emergent infusion related reaction. Of these 44% (173/395) took preventive medications and 56% (222/395) did not. Of those that took preventive medications, 39% (68/173) had one or more subsequent infusion related reactions. Of those that did not take preventive medications, 29% (64/222) had one or more subsequent infusion related reactions. *(Sources: Sponsor Tables 13.3.2.6.8 Ole and Table 14.3.2.6.7. OLE submitted on April 20, 2023, in response to an IR from the Agency).*

201 OLE

With a data cut off of December 1, 2022, the total number of infusion related reactions in 201 OLE is 38 (up from 37 with a data cut off of April 15, 2022). This number includes 2 subjects with 2 PTs that were not coded to the PT "infusion related reaction" but were categorized as

infusion-related reaction in the AE case report form (CRF) by the investigator (PTs were pyrexia and injection site joint erythema).

In the OLE there was one SAE (b) (6)) due to infusion related reaction, and this subject was the only discontinuation due to infusion related reaction.

I have reviewed all the infusion related reaction narratives, including for those that led to discontinuations. Selected narratives are provided below.

301 Core

(b) (6)

81-year-old male who, on the first day of infusion prior to the infusion was noted to have mild thrombocytopenia (136,000). During the infusion, he became cyanotic, and had rigors and fever of 38.8° C. He was transferred to the emergency room, where he received diphenhydramine and intravenous saline. He was diagnosed with a Grade 3, severe and serious infusion related reaction. While cyanosis improved, he had recurrent fever and rigors. He received famotidine, glucose, ondansetron, and paracetamol. Study Drug was permanently discontinued due to thrombocytopenia and infusion related reaction. Infusion related reaction resolved on study day 2.

(b) (6)

73-year-old female who had a relevant past medical history of hypercholesterolemia, hypertension and cardiac murmur. According to the narrative, the subject had a chest CT showing right lower lobe consolidation, and hypoxia suggestive of pneumonia 165 days before first dose of study drug. During screening her blood pressure was 144/68 mmHg, temperature 37.1° C. Her ECG was normal. On study day 1 on the day of the first infusion, the subject complained of feeling chills, and achiness, and the infusion was stopped. She was experiencing acute respiratory failure and hypoxia, which was classified as a Grade 3 infusion related reaction. It was severe and serious, and she was hospitalized. At the hospital, the subject reported feeling fatigue and shortness of breath a few days prior to presenting to the hospital. She received treatment with diphenhydramine, and paracetamol. A few hours later she recovered from these symptoms, but shortly thereafter she was noted to be pale with an oxygen saturation of 83 %. She was treated with oxygen, iv saline, azithromycin, ceftriaxone, and furosemide. Oxygen had to be delivered continuously because her oxygen saturation would drop when supplemental oxygen was removed. The infusion was not resumed. She was also noted to have a temperature of 38.4° C. A chest x-ray at the hospital showed increased pulmonary vascular prominence and streaky opacities left greater than right suggestive of mild pulmonary edema, atelectasis and aspiration or pneumonia. She also had elevated brain natriuretic peptide of 648 pg/ml, and low potassium (3.2). The laboratory results showed low lymphocyte percentage of 2.4% (NR: 15-48%), high neutrophil percentage of 95.5% (NR: 40-75%), white blood cell of 6.66 k/µL (NR: 3.8-11 k/µL), and brain natriuretic peptide of 648 pg/mL (normal value: 100 pg/mL). SARS COV- 2 and respiratory pathogen panels were

negative. An echocardiogram showed normal ejection fraction of 65% with mildly elevated pulmonary pressures and trace mitral and mild tricuspid regurgitation. The event of infusion related reaction resolved on study day 3, and the subject was discharged from the hospital. During discharge, her oxygen saturation level was 96%.

Reviewer Comment: While the subject's symptoms occurring right after the infusion are highly supportive of an infusion related reaction, she did report at the hospital feeling fatigued and short of breath few days prior to the infusion. I cannot rule that she experienced an infusion related reaction which was superimposed on a pre-existing pulmonary infection. Of note, low lymphocytes post-infusion were a laboratory finding in 201 Core.

(b) (6)

74-year-old male who on study day 1, about 40 minutes after the infusion experienced vomiting, mild nausea, dyspnea with increased respiratory rate, retraction and basal wheezing. It was classified as severe and serious and as a Grade 4 infusion related reaction. He was given 4 puffs of salbutamol (patient's own medication). He also experienced back stiffness and pain, and increased chills and cold extremities. He was treated with diphenhydramine. He had continued to vomit with increased chills. He was treated with epinephrine. The infusion related reaction was considered to be an anaphylactic reaction as involved two systems the respiratory system ("sibilance" [hissing sound], dyspnea and CO_2 accumulation) and digestive system with persistent nausea and vomiting. There was no report of oral, laryngeal or facial swelling. He was taken to the ER. His symptoms gradually reduced in the ER, and on Day 2 symptoms resolved. Study Drug was permanently discontinued.

(b) (6)

66 year-old-male who approximately 4 hours after the end of the first infusion had a cold sensation in his entire body, and complained of a headache. His blood pressure was 180/85 mmHg. He was diagnosed with a Grade 3 infusion related reaction which was serious and severe. He also experienced syncope. His neurological exam was normal. He was given furosemide. His blood pressure was found to be 190/105, and his body temperature was 36.5° C. He additionally was given alprazolam for anxiety. He was transferred to the emergency room, for observation. Later that evening his symptoms resolved. Study drug was permanently discontinued.

(b) (6)

77-year-old male who experienced shivering. Blood pressure was 190/90 mmHg 2 hours after the first infusion; the narrative stated that he developed a hypertensive crisis. He had an episode of vomiting. A Grade 3 infusion related reaction was reported. He was treated with chlorphenamine, clonidine, furosemide, hydrocortisone and paracetamol. The infusion related reaction was rated as severe and serious (medically important event). He was asymptomatic 2.5 hours after symptom onset. He was discontinued from study drug due to the event of infusion related reaction.

(b) (6)

83-year-old female on the day of the first infusion (study day 1), experienced a fever of 39.3° C and low blood pressure of 98/62 mmHg. She also had erythematous plaques 1-2 mm in diameter on the legs, upper limbs, and back waits, for which she visited the ER. She was hospitalized for an infusion related reaction and rash. On study day 3 she was discharged from the hospital with improvement in the fever, and On study day 10 rash and fever resolved. On study day 4, she also experienced a bile duct stone and had syncope, which led to hospitalization briefly and discharge the same day. On study day 5, she was re-hospitalized, and diagnosed with serious adverse event of cholangitis, and treated with iv fluids and antibiotics. The study drug was permanently discontinued due to cholangitis and bile duct stone.

(b) (6)

83-year-old male who on study day 1, experienced cold and shivering after the first infusion. A Grade 2 infusion related reaction was reported. It was mild in severity and nonserious. He was treated with paracetamol and chlorphenamine. No action was taken with study drug, and the event of infusion related reaction with fever and raised blood pressure was considered resolved on study day 3. Following the second infusion on study day 97, he had increased confusion and tiredness. A Grade 3 infusion related reaction was reported. Prior to the infusion he was treated prophylactically with paracetamol. On study day 98, he reported increased tiredness and a fever of 38° C. The study drug was withdrawn due to this event.

301 OLE

(b) (6)

58-year-old male who received placebo during 301 Core participation. After the first infusion on extension day 1, the subject was noted to begin feeling light-headed, with chills, nausea and vomiting. His blood pressure was recorded to be 88/55, heart rate 75 bpm, with some tachypnea at 16 breaths per minute. His temperature was 37.2° C. Saline was administered, but he continued to have chills, shivering and emergency transportation was called to take him to the ER. He was diagnosed with a Grade 2 infusion related reaction. He was treated with diphenhydramine, ondansetron, and sodium chloride. The study drug was permanently discontinued, and his symptoms resolved the next day.

(b) (6)

59 year-old-male who received placebo during the 301 Core study, received the first dose of study drug in the 301 OLE on extension day 1. He was given diphenhydramine prophylactically to prevent an infusion related reaction. After the infusion he had chills, rigors, neck, and back pain. His fever increased to 38.7° C, and he was diagnosed with a Grade 2, moderate and serious infusion related reaction (due to medically important event designation). He received treated with paracetamol, hydrocortisone. On extension day 3, he continued to have malaise, headache and a fever of 37.7° C. He again was treated with ibuprofen and methylprednisolone.

Symptoms resolved on extension day 4. The same day he had markedly abnormal low lymphocyte value of 0.43 $x10^9$. On extension day 8, lymphocyte count returned to normal (1.22 $x10^9$). He received the second dose of study drug on extension day 12, and participation was ongoing.

(b) (6)

78-year-old male who received placebo in 301 Core. On extension day 1, after the infusion he reported having chills, pyrexia, and a grade 2, severe and serious (medically important) infusion related reaction was diagnosed. He was noted to have tachypnea and mildly elevated temperature of 37° C. He was treated with dexamethasone, sodium chloride, epinephrine, and oxygen. His symptoms resolved later the same day. He received the 12th dose of study drug on extension day 154 and participation is ongoing.

(b) (6)

55-year-old female who received placebo while on 301 Core. Two hours after the first infusion on extension day 1 was stopped the patient complained of chills and frequent eructation. Her BP was 82/71 mmHg, she was tachypneic with a heart rate of 100 bpm, and respiratory rate of 20. She was diagnosed with a Grade 2 infusion related reaction with symptoms of low blood pressure, fever, nausea and headache. It was categorized as severe and serious. She presented to the emergency department and was treated with iv fluids. She was noted to have a temperature of 38.7° C and treated with acetaminophen. Her c-reactive protein (CRP) was increased to 4.28 (no units provided in the narrative). On extension day 2 her symptoms resolved. Study drug was permanently discontinued.

12.1.11. Laboratory

Table 85 Subjects with One or more Postbaseline Hematology Value with Specified Elevated or Low Values in 301 Core

Parameter	Placebo (N = 897)	Lecanemab (N = 898)
WBC, low (<3000 cells/uL)	24 (2.7)	20 (2.2)
WBC, high (>13,000 cells/uL)	8 (0.9)	16 (1.8)
Hemoglobin, >1.5 (g/dL) decrease from baseline	108 (12.0)	90 (10.0)
Hemoglobin, >2 (g/dL) increase from baseline	24 (2.7)	27 (3.0)
Platelets, low (<125,000 cells/uL)	28 (3.1)	29 (3.2)
Differential		
Lymphocytes, low (<750 cells/uL)	79 (8.8)	71 (7.9)
Lymphocytes, high (>10000 cells/uL)	1 (0.1)	0 (0.0)
Neutrophils, low (<1000 cells/uL)	2 (0.2)	6 (0.7)

Parameter	Placebo (N = 897)	Lecanemab (N = 898)
Eosinophils, high (>1500 cells/uL)	3 (0.3)	1 (0.1)

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Table 86 Subjects with One or More Hematology Value with Specified Elevated or Low Value at End of Treatment 301 Core

Parameter	Placebo (N = 897)	Lecanemab (N = 898)
WBC, low (<3000 cells/uL)	10 (1.1)	4 (0.4)
WBC, high (>13,000 cells/uL)	2 (0.2)	3 (0.3)
Hemoglobin, >1.5 (g/dL) decrease from baseline	51 (5.7)	29 (3.2)
Hemoglobin, >2 (g/dL) increase from baseline	7 (0.8)	7 (0.8)
Platelets, low (<125,000 cells/uL)	7 (0.8)	10 (1.1)
Lymphocytes, low (<750 cells/uL)	26 (2.9)	25 (2.8)
Lymphocytes, high (>10000 cells/uL)	1 (0.1)	0 (0.0)
Neutrophils, low (<1000 cells/uL)	1 (0.1)	1 (0.1)
Eosinophils, high (>1500 cells/uL)	2 (0.2)	1 (0.1)

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Table 87 Subjects with One or More Chemistry Value with Specified Elevated or Low Value at Any Time during the Study 301 Core

Parameter	Placebo (N = 897)	Lecanemab (N = 898)
Sodium, low (<130mEq/L)	8 (0.9)	14 (1.6)
Sodium, high (>155 mEq/L)	1 (0.1)	0 (0.0)
Potassium, low (<3.4 mEq/L)	30 (3.3)	31 (3.5)
Potassium, high (>6 mEq/L)	4 (0.4)	4 (0.4)
Chloride, low (<88 mEq/L)	2 (0.2)	1 (0.1)
Chloride, high (>112 mEq/L)	1 0.1)	7 (0.8)
Bicarbonate, low (<18 mEq/L)	10 (1.1)	13 (1.4)
Bicarbonate, high (>30 mEq/L)	60 (6.7)	48 (5.3)

Parameter	Placebo (N = 897)	Lecanemab (N = 898)
Blood urea nitrogen, high (>27 mg/dL)	115 (12.8)	89 (9.9)
Glucose, low (<54 mg/dL)	9 (1.0)	16 (1.8)
Glucose, high Fasting (>= 126 mg/dL) or Random (>= 200 mg/dL)	68 (7.6)	73 (8.1)
Calcium, low (<8 mg/dL)	7 (0.8)	17 (1.9)
Calcium, high (>11 mg/dL)	1 (0.1)	0 (0.0)
Phosphate, low (<2 mg/dL)	7 (0.8)	8 (0.9)
Protein (total), low (<5.4 g/dL)	6 (0.7)	14 (1.6)
Albumin, low (<2.5 g/dL)	1 (0.1)	1 (0.1)
Creatinine, high (mg/dL) >=2.0 x baseline	2 (0.2)	0 (0.0)

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Table 88 Subjects with One or More Chemistry Value with Specified Elevated or Low Value at End of Treatment 301 Core

Parameter	Placebo (N = 897)	Lecanemab 10mg/bi-weekly (N = 898)
Sodium, low (<130mEq/L)	1 (0.1)	5 (0.6)
Sodium, high (>155 mEq/L)	0 (0.0)	0 (0.0)
Potassium, low (<3.4 mEq/L)	5 (0.6)	5 (0.6)
Potassium, high (>6 mEq/L)	0 (0.0)	0 (0.0)
Chloride, low (<88 mEq/L)	0 (0.0)	0 (0.0)
Chloride, high (>112 mEq/L)	0 (0.0)	0 (0.0)
Bicarbonate, low (<18 mEq/L)	2 (0.2)	3 (0.3)
Bicarbonate, high (>30 mEq/L)	16 (1.8)	9 (1.0)
Blood urea nitrogen, high (>27 mg/dL)	43 (4.8)	34 (3.8)
Glucose, low (<54 mg/dL)	1 (0.1)	2 (0.2)
Glucose, high Fasting (>= 126 mg/dL) or Random (>= 200 mg/dL)	19 (2.1)	23 (2.6)
Calcium, low (<8 mg/dL)	1 (0.1)	3 (0.3)

Parameter	Placebo (N = 897)	Lecanemab 10mg/bi-weekly (N = 898)
Calcium, high (>11 mg/dL)	0 (0.0)	0 (0.0)
Phosphate, low (<2 mg/dL)	2 (0.2)	2 (0.2)
Protein (total), low (<5.4 g/dL)	1 (0.1)	0 (0.0)
Albumin, low (<2.5 g/dL)	1 (0.1)	0 (0.0)
Creatinine, high (mg/dL) >=2.0 x baseline	2 (0.2)	0 (0.0)
Alkaline phosphatase, high (U/L) >2.0 x ULN	5 (0.6)	0 (0.0)
Alanine Aminotransferase, high (U/L) >5.0 x ULN	1 (0.1)	0 (0.0)
Aspartate Aminotransferase, high (U/L) >5.0 x ULN	0 (0.0)	0 (0.0)
Bilirubin (total), high (mg/dL) >2.0 x ULN	1 (0.1)	2 (0.2)

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Table 89 Subjects with One or More Hematology Value with Specified Elevated or Low Values in 301 OLE

Parameter	Lecanemab (N =1612)
WBC, low (<3000 cells/uL)	31 (1.9)
WBC, high (>13,000 cells/uL)	22 (1.4)
Hemoglobin, >1.5 (g/dL) decrease from baseline	130 (8.1)
Hemoglobin, >2 (g/dL) increase from baseline	37 (2.3)
Platelets, low (<125,000 cells/uL)	42 (2.6)
Lymphocytes, low (<750 cells/uL)	103 (6.4)
Lymphocytes, high (>10000 cells/uL)	1 (0.1)
Neutrophils, low (<1000 cells/uL)	7 (0.4)
Eosinophils, high (>1500 cells/uL)	2 (0.1)

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Table 90 Subjects with One or More Chemistry Value with Specified Elevated or Low Values in 301 OLE

Parameter	Lecanemab (N =1612)
Sodium, low (<130mEq/L)	16 (1.0)
Sodium, high (>155 mEq/L)	0 (0.0)

Parameter	Lecanemab (N =1612)
Potassium, low (<3.4 mEq/L)	45 (2.8)
Potassium, high (>6 mEq/L)	7 (0.4)
Chloride, low (<88 mEq/L)	2 (0.1)
Chloride, high (>112 mEq/L)	9 (0.6)
Bicarbonate, low (<18 mEq/L)	14 (0.9)
Bicarbonate, high (>30 mEq/L)	59 (3.7)
Blood urea nitrogen, high (>27 mg/dL)	137 (8.5)
Glucose, low (<54 mg/dL)	19 (1.2)
Glucose, high Fasting (>= 126 mg/dL) or Random (>= 200 mg/dL)	102 (6.3)
Calcium, low (<8 mg/dL)	22 (1.4)
Calcium, high (>11 mg/dL)	2 (0.1)
Phosphate, low (<2 mg/dL)	15 (0.9)
Protein (total), low (<5.4 g/dL)	21 (1.3)
Albumin, low (<2.5 g/dL)	2 (0.1)
Creatinine, high (mg/dL) >=2.0 x baseline	0 (0.0)
Alkaline phosphatase, high (U/L) >2.0 x ULN	4 (0.2)
Alanine Aminotransferase, high (U/L) >5.0 x ULN	1 (0.1)
Aspartate Aminotransferase, high (U/L) >5.0 x ULN	0 (0.0)
Bilirubin (total), high (mg/dL) >2.0 x ULN	4 (0.2)

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Table 91 Maximum Post Baseline Liver Enzymes in Study 301 Core

Lab Test	Cut point	Placebo (n=897) n(%)	Lecanemab (n=898) n(%)
ALT	>3 ULN	9 (1)	10 (1)
	>5 ULN	4(0.4)	1 (0.1)
	>10 ULN	1 (0.1)	0
	Missing	2 (0.2)	9 (1)
AST	>3 ULN	6 (0.7)	7 (0.8)
	>5 ULN	2(0.2)	0
	>10ULN	1(0.2)	0
	Missing	2(0.2)	9 (1)

ALP	> 2 ULN >5 ULN Missing	7(0.8) 1(0.1) 2(0.2)	3 (0.3) 1 (0.1) 9 (1)
BILI	>2 ULN Missing	3(0.3) 2(0.2)	3(0.3) 9 (1)

Source: extracted from analysis results by clinical analyst using JMP clinical

Table 92 Aminotransferase Elevation and Possible Hy's Law Cases

		Placebo		Lecanemab	
Elevated Aminotransferase Tests	**Possible Hy's Law Case**	**Subject Count**	**% of Subjects**	**Subject Count**	**% of Subjects**
Yes	Yes	1	0.1%	0	0.0%
Yes	No	9	1.0%	13	1.5%
No	No	885	98.9%	876	98.5%

Source: extracted from analysis results by clinical analyst using JMP clinical
**Elevated AT Tests defined as ALT or AST >= 3*ULN.*
**Possible Hy's Law Case defined as ALT or AST >= 3*ULN and BILI >= 2*ULN within 0 Days of ALT/AST elevation*

12.1.12. Vital signs and ECG

Table 93 Shifts in ECG from Baseline to One or More Abnormal Postbaseline Value

Treatment	Baseline	Normal	Abnormal NCS
Placebo (N = 897)	Normal	362 (40.8%)	149 (16.8%)
	Abnormal NCS	17 (1.9%)	318 (35.8%)
	Abnormal CS	0 (0.0%)	2 (0.2%)
Lecanemab 10mg/bi-weekly (N = 898)	Normal	390 (45.2%)	126 (14.6%)
	Abnormal NCS	13 (1.5%)	289 (33.5%)
	Abnormal CS	0 (0.0%)	0 (0.0%)

Subjects had baseline and at least one postline results.
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NCS: Not clinically significant
CS: clinically significant

12.1.13. Management of ARIA-E and ARIA-H in Studies 303 A3 and 303 A45

Table 4 Actions Required for Subjects With ARIA-H

Symptoms or Radiology Findings	Study Drug Action	Required Follow-Up Safety Visits with MRI	Resumption of Treatment
Asymptomatic microhemorrhages	None	Case by case basis, as discussed with medical monitor	N/A
Asymptomatic superficial siderosis	None	Case by case basis, as discussed with medical monitor	N/A
Symptomatic microhemorrhages/symptomatic superficial siderosis/single macrohemorrhage (>10 mm), symptomatic or not	Drug administration temporarily stopped at 1st occurrence in the study [a] Study drug must be discontinued after the 2nd occurrence in the study	At approximately 30 days (as unscheduled or scheduled visits) after the event was identified. Further safety visits (with MRI) will occur at approximately every 30 days (as unscheduled or scheduled visits) until the event has stabilized radiographically and symptoms have resolved	Treatment may resume upon resolution/stabilization of events, resumption of treatment following the occurrence of events can only occur once

ARIA-H = amyloid-related imaging abnormality - hemorrhage, MRI = magnetic resonance imaging, N/A = not applicable
a: During treatment interruption, subjects should undertake all regularly scheduled assessments as described in the Schedule of Assessments.

Table 5 Actions Required for Subjects With ARIA-E (revised per Amendment 04)

Symptoms or Radiology Findings	Study Drug Action	Required Follow-Up Safety Visits with MRI	Resumption of the Treatment
Asymptomatic, radiographically mild	None	At approximately 30, 60, and 90 days (as unscheduled or scheduled visits) after the event was identified, even if resolved, then MRI will be performed as per Schedule of Assessments.	N/A
Symptomatic or radiographically moderate or severe	Drug administration temporarily stopped at 1st occurrence in the study[a] unless considered an SAE, in which case will be permanently discontinued Study drug must be discontinued after the 2nd occurrence in the study	At approximately 30 days, then 90 days (as unscheduled or scheduled visits) after first identification, even if resolved, and every 30 days (as unscheduled or scheduled visits) until the ARIA-E has resolved radiologically or clinically.	Resumption of the treatment when resolved radiologically and clinically; can occur once during the course of the treatment

ARIA-E = amyloid-related imaging abnormality edema/effusion, MRI = magnetic resonance imaging, N/A = not applicable, SAE = serious adverse event
a: During treatment interruption, subjects should undertake all regularly scheduled assessments as described in the Schedule of Assessments.

12.1.14. Safety Analysis Plan and Definitions

In addition to the safety analysis plans outlined in Section 7.3.2, the following criteria were in place in the protocol for analysis of adverse events.

The criteria for identifying AEs in this study were:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the investigational product (Note: Every sign or symptom was not listed as a separate AE if the applicable disease (diagnosis) was being reported as an AE)
- Any new disease or exacerbation of an existing disease
- Any deterioration in non protocol-required measurements of a laboratory value or other clinical test (e.g., ECG or x-ray) that resulted in symptoms, a change in treatment, or discontinuation of study drug
- Recurrence of an intermittent medical condition (e.g., headache) not present pretreatment (Baseline)
- An abnormal laboratory test result was considered an AE if the identified laboratory abnormality led to any type of intervention, withdrawal of study drug, or withholding of study drug, whether prescribed in the protocol or not

All AEs, regardless of relationship to study drug or procedure, were recorded beginning from the time the subject signed the study informed consent form (ICF) through the last assessment (Visit 42 for the Core Study). AEs were collected for up to 3 months after the last dose or through the last assessment, whichever was longer. This included those subjects who discontinued from study drug and who returned for regularly scheduled visits where clinical assessments were conducted.

Abnormal laboratory values were not to be listed as separate AEs if they were considered to be part of the clinical syndrome that was being reported as an AE. It was the responsibility of the investigator to review all laboratory findings in all subjects and determine if any laboratory results constituted an AE. Medical and scientific judgment was exercised in deciding whether an isolated laboratory abnormality was classified as an AE. Any laboratory abnormality considered to constitute an AE was reported on the Adverse Event CRF.

Abnormal ECG (corrected QT interval [using Fridericia's Formula, QTcF]) results, if not otherwise considered part of a clinical symptom that was being reported as an AE, were considered an AE if (1) the QTcF interval was more than 450 ms and there was an increase of more than 60 ms from baseline, or (2) the QTcF interval was more than 500 ms. Any ECG abnormality that the investigator considered as an AE was reported as such.
It was the responsibility of the investigator to review the results the C-SSRS for all subjects

and determine if any result constituted an AE. Medical and scientific judgment was exercised in deciding whether an isolated suicidality rating scale response should be classified as an AE (Section 9.5.1.4.9.2 provides a description of the C-SSRS).
All AEs were followed for 90 days after the subject's last dose, or until resolution, whichever came first. All SAEs were followed to resolution or, if resolution was unlikely, to stabilization.

In 301 Core, a TEAE was defined as an AE that emerges during treatment or within 90 days of the last dose of study drug, having been absent at pretreatment (Baseline) or:

- Reemerges during treatment, having been present at pretreatment (Baseline) but stopped before treatment, or
- Worsens in severity during treatment relative to the pretreatment state, when the AE is continuous.

In the combined 301 Core and OLE Study, similar to the combined 201 Core and OLE ISS dataset, the sponsor defined a TEAE as emerging within 30 days of last administration

Reviewer Comment: A TEAE definition of occurring within 30 days after the last dose of study drug is reasonable, given the 5-day half-life of study drug (albeit a longer pharmacodynamic (PD) half-life).

The overall approach to assessing relationship of AE to study treatment is acceptable and was based on the following:

- Temporal relationship of the onset of the event to the initiation of the study treatment
- The course of the event, especially the effect of discontinuation of study treatment or reintroduction of study treatment, as applicable
- Whether the event was known to be associated with the study treatment or with other similar treatments
- The presence of risk factors in the study subject known to increase the occurrence of the event
- The presence of non-study, treatment-related factors that are known to be associated with the occurrence of the event

An SAE was defined as any untoward medical occurrence that at any dose:

- Resulted in death
- Was life-threatening (ie, the subject was at immediate risk of death from the AE as it occurred; this did not include an event that, had it occurred in a more severe form or was allowed to continue, might have caused death)
- Required inpatient hospitalization or prolongation of existing hospitalization
- Resulted in persistent or significant disability/incapacity
- Was a congenital anomaly/birth defect (in the child of a subject who was exposed to the study drug)

Other important medical events that may not have been immediately life-threatening or resulted in death or hospitalization but, when based on appropriate medical judgment, may have jeopardized the subject, or may have required intervention to prevent one of the outcomes in the definition of SAE listed above were also to be considered SAEs. Medical and scientific judgment was exercised in deciding whether expedited reporting was appropriate in such situations.

In addition to the above, other events associated with special situations included pregnancy or exposure to study drug through breastfeeding; AEs associated with study drug overdose, misuse, abuse, and medication error. These events associated with special situations were captured using the SAE procedures but were considered as SAEs only if they met one of the above criteria. All AEs associated with special situations were reported on the CRF whether or not they met the criteria for SAEs.

Study specific AEs of interest included ARIA-E, ARIA-H (macrohemorrhages, superficial siderosis, or new cerebral microhemorrhages), infusion related reactions, hypersensitivity reactions, a "yes" response to C-SSRS suicidal ideation Type 4 or 5.

Adverse events were coded using MedDRA Version 25 for Study 301 and MedDRA Version 24.0 for the OLE. There were 109 records (21%) that were mismatched for the Preferred Term and 5 records (0.99%) mismatched for the Body System and Organ Class Term between 201 Core and ISS. Mismatches caused by differences in the MedDRA versions were reviewed individually, to identify any mismatch that may impact AE identification. None were found to impact the safety assessment.

The following sponsor table (Table 94) describes the list of preferred terms for Adverse Events of Special Interest:

Table 94 List of Preferred Terms For Adverse Events of Special Interest – Core Study

AE of Special Interest	Preferred Term – MedDRA: 25.0
ARIA-E	Amyloid related imaging abnormality-edema/effusion
ARIA-H	
Macrohemorrhage	Cerebral hemorrhage Hemorrhage intracranial Thalamus hemorrhage
Superficial siderosis	Superficial siderosis of central nervous system
Cerebral microhemorrhage	Amyloid related imaging abnormality- microhemorrhage and hemosiderin deposit[a] Cerebellar microhemorrhage
Infusion-related reactions	Infusion-related reaction
Skin rash	Rash[b]

Other hypersensitivity reactions	Hypersensitivity[b] Immediate post-injection reaction[b] Infusion-related hypersensitivity reaction[b] Infusion site hypersensitivity[b]
Suicidal behavior	Completed suicide Depression suicidal Intentional overdose Intentional self-injury Poisoning deliberate Suicidal behavior Suicide attempt Suicide threat Assisted suicide Suspected suicide Suspected suicide attempt
Suicidal ideation	Self-injurious ideation Suicidal ideation

(Source BAN2401-G000-301 CSR Table 1) AE = adverse event, ARIA-E = amyloid related imaging abnormality-edema/effusion, ARIA-H = amyloid related imaging abnormality- microhemorrhage and hemosiderin deposit, MedDRA = medical dictionary for regulatory activities.
a: This preferred term was not used for superficial siderosis.
b: Relationship to study drug should be yes to the question 'Is there a reasonable possibility that the study drug caused the adverse event' in this study to be considered as AE of special interest.
Source: Appendix 16.1.9, SAP Appendix 13.2.

Routine Clinical Tests

Vital Signs:

Vital sign measurements (i.e., systolic and diastolic blood pressure [BP] [mmHg], pulse [beats per minute], respiratory rate [per minute], body temperature [in centigrade]), and weight (kg) were obtained at the visits designated in the Schedule of Assessments (Protocol Section 9.5.2 in Appendix 16.1.1) by a validated method. All vital signs were measured after the subject had been in a semi-supine position for 3 minutes. Whenever possible, BP measurements were performed on the same arm and by the same investigator. Vital signs were measured both at predose and after infusion. During Study Visits 3, 4, 5, and 6, vital signs were obtained at least 2 hours after infusion. If at those visits no untoward effects of infusions on vital signs were detected ≥2 hours after infusion, these assessments at subsequent study visits were conducted at a shorter interval after infusion. At visits where no infusion takes place (e.g., Visit 43), vital signs were measured once.

Laboratory Tests

The clinical laboratory tests performed are summarized in Table 95. The Schedule of Assessments (Protocol Section 9.5.2 in Appendix 16.1.1) shows the visits and time points at which blood for clinical laboratory tests and urine for urinalysis were collected in the study. Blood for laboratory tests were taken predose at all visits as indicated.

Table 95 Clinical Laboratory Tests (revised per Amendment 06)

Category	Parameters
Hematology	hematocrit, hemoglobin, platelets, RBC count, and WBC count with differential (bands, basophils, eosinophils, lymphocytes, monocytes, neutrophils)
Chemistry	
Electrolytes	bicarbonate, calcium, chloride, potassium, sodium
Liver function tests	alanine aminotransferase, alkaline phosphatase, aspartate aminotransferase, direct bilirubin, gamma glutamyl transpeptidase, total bilirubin
Renal function parameters	blood urea/blood urea nitrogen, creatinine
Other	albumin, cholesterol, globulin, glucose, lactate dehydrogenase, phosphorus, total protein, triglycerides, uric acid
Urinalysis	color, appearance, bacteria, casts, crystals, epithelial cells, glucose, ketones, occult blood, pH, protein, RBCs, specific gravity, WBCs, bilirubin, urobilinogen, yeast, nitrite, leucocyte esterase (revised per Amendment 04)
Other	at Screening only: free T3, free T4, TSH, Vitamin B12 (and MMA, where available), clotting screen (prothrombin time [PT, INR], activated partial thromboplastin time) Anytime during the study: HbA1c[a] (as needed)

HbA1c = hemoglobin A1c, INR = international normalized ratio, MMA = methylmalonic acid, PT = prothrombin time, RBC = red blood cell, T3 = triiodothyronine, T4 = thyroxine, TSH = thyroid stimulating hormone, WBC = white blood cell.

[a] Will be performed only as needed, at the clinical discretion of the investigator. (revised per Amendment 06)

Source: Table 4 from Protocol BAN2401-G000-301 Version 12.0/24 Aug 2022 (per Amendment 10)

Laboratory test results are assigned a low/normal/high (LNH) classification according to whether the value was below (L), within (N), or above (H) the laboratory parameter's reference range.

The Applicant used the Common Toxicity Criteria for Adverse Events v4.0.3 (CTCAE) published on June 14, 2010, to determine grade for laboratory tests (Appendix Table 81).

The sponsor relied on the CTCAE criteria to identify subjects with treatment-emergent markedly abnormal laboratory values (TEMAVs). Except for phosphate, a TEMAV was defined by the sponsor as a postbaseline value with an increase from baseline to a grade of 2 or higher. For phosphate, a TEMAV was defined as a postbaseline value with an increase from baseline to a grade of 3 or higher. Since the CTCAE criteria are created for clinical trials in cancer, reliance on the CTCAE grading alone for some of the laboratory values may miss some clinically significant laboratory findings that are not included in the CTCAE grading. For example, elevation in white cell count, is not captured by the CTCAE grading system above, but may be important in non-cancer trials.

Reviewer Comment: To be able to capture clinically significant abnormal values that may not be captured as part of the CTCAE grading system (such as a shift to abnormally high neutrophil

count), the review of laboratory values will include thresholds identified by the FDA as clinically significant.

ECGs:
During Study 301 Core, single ECGs were obtained as designated in the Schedule of Assessments (Appendix 12.1.1). If QTcF was found to be out of range, 2 additional ECGs were done to allow evaluation of triplicate ECGs. If an ECG abnormality met criteria of an AE as described in the protocol the AE corresponding to the ECG abnormality will be recorded on the Adverse Events CRF (revised per Amendment 01).

12.1.15. Grading and Management of Infusion Related Reactions in Study 301 Core

NCI CTCAE (Version 4.0) Grading of infusion related reactions within 24 hours of infusion in Study 301 Core was as follows:

• Grade 1: mild reaction, infusion interruption not indicated, intervention not indicated
• Grade 2: infusion interruption or treatment indicated, but responds promptly to symptomatic treatment (e.g., antihistamines, nonsteroidal anti-inflammatory drugs, IV fluids); prophylactic medications indicated for <24 hours
• Grade 3: prolonged (e.g., not rapidly responsive to symptomatic medications or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization required for clinical sequelae (e.g., renal impairment)
• Grade 4: life-threatening consequences; urgent treatment needed (eg, vasopressor or ventilatory support)
• Grade 5: death

Management guidelines of infusion related reactions in Study 301 core included stopping the infusion, treatment with diphenhydramine or dexamethasone, or other antihistamines, corticosteroids, anti-inflammatory medications, bronchodilators, IV fluids, IV adrenaline, or other medications as indicated. For Grade 2 infusions, the infusion could be resumed at 50% of the prior rate if the reaction improved or resolved. For Grade 3 or 4 reactions, the subject was discontinued from study drug.

12.2. References

See in text references

12.3. Financial Disclosure

See clinical efficacy review by Dr. Kevin Krudys for Financial Disclosures.

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/

DENIZ ERTEN-LYONS
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RANJIT B MANI
07/05/2023 06:57:15 PM

SALLY U YASUDA
07/05/2023 06:59:29 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761269Orig1s001

PRODUCT QUALITY REVIEW(S)

Memorandum of Assessment:

Submission Tracking Number (STN):	761269 (0125/EDR0120)
Subject:	Supplemental BLA: Introduction of the final clinical study report for Study BAN2401-G000-301 (Study 301) as the confirmatory clinical trial verifying the clinical benefit of lecanemab.
Date Received:	January 6, 2023
Assessment/Revision Date:	June 8, 2023
Primary Assessor:	Gunther H. Boekhoudt, Ph.D., Product Quality Assessor CDER/OPQ/OBP/DBRR IV
Secondary Assessor:	Samuel Mindaye, Ph.D., Team Lead, CDER/OPQ/OBP/DBRR IV
Tertiary Assessor:	N/A
RBPM:	Janell Artis, CDER/OPQ/OPRO
Consults:	N/A
Applicant:	Eisai, Inc.
Product:	LEQEMBI (Lecanemab)
Indication:	For the treatment of Alzheimer's disease
Filing Action Date:	March 10, 2023
Action Due Date:	July 6, 2023

1. Summary Basis of Recommendation:

a. Recommendation:

Approvability of this supplement is deferred to OND.

b. Justification:

In this supplement, Eisai submits the final clinical study report for Study BAN2401-G000-301 (Study 301) as the confirmatory clinical trial verifying the clinical benefit of lecanemab. In addition, Eisai provided (b) (4) [redacted] which is inadequate, and the applicant agreed to address this problem in PMR# 4384-2). (b) (4) [redacted]

2. Suggested Language for Action Letter:

Action letter language is deferred to OND.

3. Assessment:

This supplement BLA contains the final results for the above-mentioned clinical studies and does not contain any new CMC information. (b) (4)

Assessor Comment:

No changes to the lecanemab manufacturing process, controls, release and stability specifications were introduces.

(b) (4)

However, Clinical Pharmacology and the sponsor agreed on a post-marketing requirements (PMR # 4384-2) to increase the drug tolerance and sensitivity of the assay.

(b) (4)

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(b) (4)

[redacted]

Environmental Assessment or Claim of Categorical Exclusion
Regeneron requested categorical exclusion from the requirements of environmental assessment pursuant to the provisions provided under 21 CFR 25.31(c).

Assessor Comment:
The categorical exclusion request from the requirement to submit an environmental assessment is acceptable.

4. **Assessment conclusions:**
This supplement contains no new CMC information and does qualify for categorical exclusion. I recommend approval of this supplement.

5. **Future Inspection Items:**
None.

6. **Status of PMC/PMR:**
N/A

Gunther Boekhoudt

Digitally signed by Gunther Boekhoudt
Date: 6/30/2023 04:25:01PM
GUID: 508da6d7000262c4c5e3578cc0a15fbf

Samuel Mindaye

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Date: 6/30/2023 04:27:00PM
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/s/

JANELL C ARTIS
07/06/2023 03:29:41 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761269Orig1s001

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #: 761269 (0120)

Drug Name: BAN2401/Lecanemab
Indication(s): Alzheimer's
Applicant: Eisai
Date(s): January 6, 2023

Review Priority:

Biometrics Division: I
Statistical Reviewer: Tristan Massie, Ph.D.
Concurring Reviewers: John Lawrence, Ph.D., Team Leader
James (Hsien-Ming) Hung, Ph.D., Division Director
Medical Division: Division of Neurology I
Clinical Team: Kevin Krudys, Ph.D.
Ranjit Mani, M.D.
Project Manager: Andrew Papanastasiou

Keywords: post-accelerated approval confirmatory study

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1 EXECUTIVE SUMMARY

At the Type B breakthrough determination (BTD)Multidisciplinary meeting held on 10 Sep 2021, the FDA agreed that the proposed biomarker and data efficacy from Study 201 Core and OLE Phase could support a Biologics License Application (BLA) submission for lecanemab under the accelerated approval pathway and that Study 301 could serve as the confirmatory study to verify the clinical benefit of lecanemab.

In January 2023, lecanemab received accelerated approval based on the effect on amyloid in study 201.

Based on highly significant results on the primary endpoint, CDR-SB, at Week 79 as well as multiplicity controlled key secondary endpoints, Study 301 appears to confirm the clinical benefit of lecanemab in early AD.

2 INTRODUCTION

2.1 Overview

The IND for this drug development of lecanemab, also referred to as BAN2401 during development, is IND 105081. There is one completed phase 2 study, study 201 and a completed phase 3 study, study 301. At the Type B BTD Multidisciplinary meeting held on 10 Sep 2021, the FDA agreed that the proposed biomarker and data efficacy from Study 201 Core and OLE Phase could support a Biologics License Application (BLA) submission for lecanemab under the accelerated approval pathway and that Study 301 could serve as the confirmatory study to verify the clinical benefit of lecanemab.

In January 2023, Lecanemab received accelerated approval based on the effect on amyloid in study 201.

Study 301 has been submitted to confirm the clinical benefit of lecanemab in early AD.

Table 1. Double Blind Phase 2/3 Placebo Controlled Study Characteristics

Study Name	Phase and Design	Treatment Period	Follow-up Period	# of Subjects per Arm	Study Population
201 (basis for accelerated approval decision)	Bayesian Adaptive Randomization Design. Randomization ratio could be changed at numerous interim analyses.	18 months	18 months	ITT/PET Pl 245/ 99 2.5 bw 52/ 28 5 mth 51 /28 5 bw 92/ 27 10mth 253/ 89 10 bw 161 /44	Alzheimer's
301 (confirmatory study)	Randomized, double blind, Parallel group	18 months	18 months	897placebo 898 10 mg/kg biweekly lecanemab	Early Alzheimer's

Note: bw=bi-weekly and mth=monthly

The BAN2401-G000-301 (Study 301) is an 18 month treatment (Core Study), multicenter, double-blind, placebo controlled, parallel-group study in subjects with Early Alzheimer's [EAD] (MCI due to AD with intermediate likelihood/Prodromal AD or mild AD dementia) with confirmed amyloid pathology indicated by either positive amyloid load confirmed by amyloid PET assessment or CSF assessment of t-tau/ Aβ[1-42].

2.2 Data Sources

The primary endpoint data set for the completed phase 3 confirmatory study, 301, is located as follows. \\CDSESUB1\evsprod\BLA761269\0120\m5\datasets\ban2401-g000-301\analysis\adam\datasets\adcdr.xpt.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The submitted data and analysis quality appear adequate.

3.2 Evaluation of Efficacy

BAN2401-G000-301

3.2.1.1 Study Design and Endpoints

Primary Objective
• To evaluate the efficacy of BAN2401 in subjects with early Alzheimer's disease (EAD) by determining the superiority of BAN2401 compared with placebo on the change from baseline in the Clinical Dementia Rating–Sum of Boxes (CDR-SB) at 18 months of treatment

Key Secondary Objectives
• To determine whether BAN2401 is superior to placebo in reducing brain amyloid levels as measured by amyloid positron emission tomography (PET) using Centiloids at 18 months
• To evaluate the efficacy of BAN2401 in subjects with EAD by determining the superiority of BAN2401 compared with placebo on the change from baseline in the Alzheimer's Disease Assessment Scale-Cognitive Subscale 14-item version (ADASCog14) at 18 months of treatment
• To evaluate the efficacy of BAN2401 in subjects with EAD by determining the superiority of BAN2401 compared with placebo on the change from baseline in the Alzheimer's disease (AD) composite score (ADCOMS) at 18 months of treatment
• To evaluate the efficacy of BAN2401 in subjects with EAD by determining the superiority of BAN2401 compared with placebo on the change from baseline in the Alzheimer's Disease Cooperative Study-Activities of Daily Living Scale for Mild Cognitive Impairment (ADCS MCI-ADL) at 18 months of treatment

Study Design
BAN2401-G000-301 (Study 301) is an 18 month treatment (Core Study), multicenter, double blind, placebo controlled, parallel-group study with an open-label extension phase in subjects with EAD (mild cognitive impairment [MCI] due to AD with intermediate likelihood/Prodromal AD or mild AD dementia) with confirmed amyloid pathology indicated by either positive amyloid load confirmed by amyloid PET assessment or CSF assessment of t tau/Aβ[1-42]. Approximately 1766 subjects were to be randomized in the Core Study across 2 treatment groups, (placebo and BAN2401 10 mg/kg, biweekly) according to a fixed 1:1 (placebo:BAN2401) schedule. Randomization was to occur across 2 clinical subgroups (MCI due to AD/prodromal AD or mild AD dementia), and was to be reasonably balanced, such that not less than approximately 50% of total number of subjects were to be in the MCI due to AD clinical subgroup. Subjects were to be stratified according to clinical subgroup; presence or

absence of ongoing approved AD treatment (e.g, acetylcholinesterase inhibitors [AChEIs], memantine, or both); apolipoprotein E4 (APOE4) status (ie, APOE4 carriers or noncarriers); and geographical region (North America, Europe [including Australia], Asia Pacific [excluding China], and China). Treatment in the Core Study was to be for 18 months (a 1-month window and related scheduling changes were to be applied if required for logistical purposes).

DETERMINATION OF SAMPLE SIZE
The sample size for this study is estimated based on comparison of BAN2401 versus placebo with respect to the primary efficacy endpoint, the change from baseline in CDR-SB at 18 months. Based on data from BAN2401-G000-201 (Study 201), an estimated standard deviation of the change from baseline CDR-SB at 18 months in placebo is 2.031 and an estimated treatment difference is 0.373 in all subjects. Therefore, assuming an estimated 20% dropout rate at 18 months in this study, a total sample size of 1566 subjects, including 783 subjects in placebo and 783 subjects in BAN2401, was expected to have 90% power to detect the treatment difference between BAN2401 and placebo in all subjects using a 2-sample t-test at a significance level of 2-sided alpha = 0.05. Considering there are about 200 subjects who missed 3 or more consecutive doses due to extenuating circumstances (eg, Coronavirus Disease 2019 [COVID-19] pandemic) with agreement with FDA on Dec 2020, approximately additional 200 subjects were to be randomized to retain 90% power, for a total sample size of approximately 1766 randomized subjects. To ensure that the study population is consistent with prior data used in the specified power calculations, no less than 70% of total number of subjects randomized were to be APOE4 carriers.
A blinded sample size re-estimation through estimated standard deviation based on blinded data before the completion of enrollment was planned to be performed if there was an indication that sample size assumptions needed to be changed. This blinded sample size re-estimation could be performed based on signals from external studies or based on review of blinded data from this study before completion of enrollment. The standard deviation of the primary endpoint was estimated based on data from Study 201. It is possible that the standard deviation for the same endpoint in this study may be larger than that due to study-to-study variation.

AMYLOID PET (IMAGING SUBGROUP)
In order to have sufficient statistical power to investigate the association between amyloid PET and clinical endpoints, this study was expected to need about 35% of the total enrolled subjects to participate in the amyloid PET subgroup.

3.2.1.2 Statistical Methodologies

Study 301 Statistical Analysis Plan

Primary Endpoint

• Change from baseline in the CDR-SB at 18 months

Key Secondary Endpoints

• Change from baseline in amyloid PET using Centiloids at 18 months for brain amyloid levels

• Change from baseline in ADAS-Cog14 at 18 months

• Change from baseline in ADCOMS at 18 months

• Change from baseline in ADCS MCI-ADL at 18 months

This study has one primary endpoint, so no adjustment for multiplicity is required for the primary analysis. If the primary endpoint is statistically significant, then the key secondary endpoints were to be tested in the following order:
(1) change from baseline in amyloid PET using Centiloids at 18 months,
(2) change from baseline in ADAS-Cog14 at 18 months,
(3) change from baseline in ADCOMS at 18 months, and
(4) change from baseline in ADCS MCI-ADL at 18 months. Each test was to be performed at a significance level of two-sided alpha=0.05 and was only to be performed if the preceding test was statistically significant.

Analysis Sets

The Randomized Set is the group of subjects who are randomized to study drug.
The Safety Analysis Set is the group of all allocated subjects who received at least one dose of study drug. At least one laboratory, vital sign, or ECG measurement obtained subsequent to at least one dose of study drug is required for inclusion in the analysis of each specific parameter. To assess change from baseline, a baseline measurement is also required. This is the analysis population used for all safety analyses which were to be based on as-treated principle.
The Full Analysis Set (FAS) is the group of randomized subjects who received at least one dose of study drug, who have a baseline assessment and at least one postdose primary efficacy measurement, and who are not randomized on or before the end date of dosing hold at the sites which have dosing hold with 6 or more weeks (≥42 days, which equal to 3 consecutive doses) during COVID-19 period of 01 Mar to 31 Jul 2020. The baseline assessment is defined as the last measurement before the first dose of BAN2401.
The FAS+ is the group of randomized subjects who received at least one dose of study drug, and who have a baseline assessment and at least one postdose primary efficacy measurement.
The Per Protocol (PP) Analysis Set is the subset of subjects in the FAS who did not miss 3 or more consecutive doses during their first 6 months in the study.

Primary Estimand

The estimand (International Council for Harmonisation of Technical Requirements of Pharmaceuticals of Human Use [ICH] E9 [R1], 2019) of the primary analysis is the mean difference of the change from baseline in CDR-SB at 18 months between treatment groups on FAS. All observed data were to be included in the primary analysis, including data collected after intercurrent events (ICH E9 [R1], 2019), i.e., initiation of new AD concomitant treatment or

change of AD concomitant treatment or treatment discontinuation. The primary analysis of the change from baseline in CDR-SB at 18 months was to be performed to compare BAN2401 versus placebo using an MMRM on the FAS. The MMRM was to include baseline CDR-SB as a covariate, with treatment group, visit, stratification variables (i.e., clinical subgroup, use of AD symptomatic medication at baseline [yes, no], APOE4 carrier status [carriers, noncarriers], and geographical region [North America, Europe, and Asia Pacific]), baseline CDR-SB-by-visit, and treatment group-by-visit interaction as fixed effects. For stratification variables, actual data (laboratory data for APOE4 carrier status, CRF data for clinical subgroup and use of AD symptomatic medication at baseline, and IxRS data for geographical region) were to be used. An unstructured covariance matrix was to be employed to model the covariance of within-subject effect; if MMRM fails to converge then a covariance structure with fewer parameters from the following list was to be employed according to the prespecified order in the list until the MMRM converges. The list of covariance structure was to include Heterogeneous Toeplitz, Heterogeneous Compound Symmetry, Toeplitz, and Compound Symmetry. If a structured covariance is used, then the sandwich estimator was to be used to estimate variance of the treatment effect estimator.

This primary analysis was to include all observed postbaseline data of the change from baseline CDR-SB without imputation of missing values. The treatment effect for BAN2401 versus placebo was to be compared at 18 months based on the MMRM. The least squares (LS) means (adjusted means) and difference in LS means (adjusted mean difference) between BAN2401 treatment and placebo, and corresponding 95% confidence interval (CI) were to be presented.

Sensitivity Analyses

The following sensitivity analyses were to be conducted to assess the robustness of the primary analysis to missing data:

• The sensitivity analysis using rank analysis of covariance (ANCOVA) after multiple imputations (MIs) at 18 months was to be performed. The imputation model was to be a regression model including the following variables: baseline and post baseline observed values, treatment group, and stratification variables (ie, clinical subgroup, use of AD symptomatic medication at baseline, APOE4 carrier status, and geographical region). Missing data was to be imputed via the imputation model using the standard MI method assuming missing at random (MAR) (Rubin 1987). After 1000 imputations with prespecified random seed (seed=2401), rank ANCOVA was to be performed using imputed datasets. The rank ANCOVA model was to include baseline CDR-SB as a covariate, with treatment group and stratification variables (ie, clinical subgroup, use of AD symptomatic medication at baseline, APOE4 carrier status, and geographical region) as factors. Analysis results from the imputed datasets were to then be combined based on Rubin’s rules (Rubin, 1987). The Hodges- Lehmann estimate of median

difference and its 95% CI were also to be calculated using imputed datasets and combined based on Rubin's rules (Rubin, 1987).

• Tipping point analysis using shift parameter (delta) separately for each treatment group based on MIs was to be performed. The missing data are first imputed by the imputation model specified from the rank ANCOVA after MIs approach (assuming missing at random) with prespecified random seed (seed=2401). To reflect the worse performance after early withdrawal, pre-specified shift parameters δ_c and δ_t are added to the imputed values for subjects on placebo and BAN2401 treatment, respectively. The adjusted multiple imputed datasets were then to be analyzed by a rank ANCOVA model and the results were to be combined using the Rubin's rule for inference. The p-value was to be provided for each pair of shift parameters (δ_c, δ_t). The robustness of the primary analysis outcomes was to be evaluated based on the scientific plausibility of the tipping point.

• The analysis using the same model as the primary analysis with just one change which is using randomization stratification variables based on IxRS classification (instead of actual data) was to be conducted.

The following supplementary analyses were to be conducted to assess the robustness of the primary analysis:

• It is postulated that BAN2401 treatment will demonstrate a clinically meaningful effect on the clinical outcome measures assessed for the overall population. However, a greater magnitude of effect is expected for the APOE4 carrier population based on the BAN2401 mechanism of action and the fact that increased levels of toxic soluble Aβ aggregate species have been noted in human APOE4 carrier pathological specimens compared to noncarriers (Hashimoto et. al., 2012, Tai et al., 2013). Further support is provided from Study 201 data. Therefore, the analysis using the same model as the primary analysis was to also be performed for the change from baseline in the CDR-SB at 18 months in APOE4 carriers on the FAS.

• The analysis using the same model as the primary analysis was to be performed on the FAS+ and the Per Protocol Analysis Set.

• The analysis using the same model as the primary analysis was to be performed on the FAS where subjects were to be censored at the time of treatment discontinuation or initiation of new AChEIs or memantine treatment regimens if they were not on AChEIs or memantine at randomization, and were to be censored at the time of dose adjustment of AChEIs or memantine if they were already on stable treatment with AChEIs or memantine at randomization.

Key Secondary Endpoints

Amyloid PET SUVR composite is a simple average of the SUVR in the following brain regions:

posterior cingulum (left and right), parietal cortex (left and right), lateral temporal cortex (left and right), and frontal cortex (left and right). Whole cerebellum is used as reference region. Amyloid PET using Centiloids is derived from this composite SUVR.

Change from baseline in amyloid PET using Centiloids at 18 months for brain amyloid levels was to be analyzed using the same MMRM as CDR-SB to compare BAN2401 versus placebo on the PD Analysis Set, using baseline amyloid PET using Centiloids and baseline amyloid PET using Centiloids-by-visit interaction in the model instead of baseline CDR-SB and baseline CDR-SB by-visit interaction.

Change from baseline in ADAS-Cog14 at 18 months

Change from baseline in ADAS-Cog14 at 18 months was to be analyzed using the same MMRM as CDR-SB to compare BAN2401 versus placebo on the FAS, using baseline ADAS-Cog14 and baseline ADAS-Cog14-by-visit interaction in the model instead of baseline CDR-SB and baseline CDR-SB-by-visit interaction. Similar models were to be used for the analyses of the key secondary endpoints ADCOMS and ADCS ADL MCI.

The relationship between the changes in CDR-SB and the changes in amyloid PET imaging were to be evaluated using correlation analysis. In the presence of strong or moderate correlation, a linear model was to be fitted to further characterize the relationship between the changes in CDRSB and the changes in amyloid PET imaging.

Correlation between clinical changes at 18 months (CDR-SB, ADAS-Cog14, ADCOMS, ADCS MCI-ADL, and modified iADRS) and change in each of the following biomarkers (amyloid PET SUVR, amyloid PET using Centiloids, tau PET SUVR and TauIQ global tau load, blood and CSF biomarkers [including but not limited to Aβ[1-42], Aβ[1-40], Aβ42/40 ratio, neurogranin [CSF only], NFL, t-tau and p-tau [including but not limited to p-tau181]], and vMRI) was to be provided on the FAS and the PD Analysis Set or the FAS+ and the PD Analysis Set. Pearson correlations and associated p-values were to be provided by treatment group and total. Pearson partial correlations adjusted for baseline value in biomarker and in clinical endpoint were also to be provided along with p-values by treatment group and total.

The primary endpoint and key secondary endpoints were to be evaluated in subgroups including age group, sex, ethnicity, geographical region, clinical subgroup (MCI due to AD, mild AD Dementia), APOE4 carrier status, APOE4 genotype (homozygous carriers, heterozygous carriers, and non-carriers), and use of symptomatic AD medication at baseline.

3.2.1.3 Patient Disposition, Demographic and Baseline Characteristics

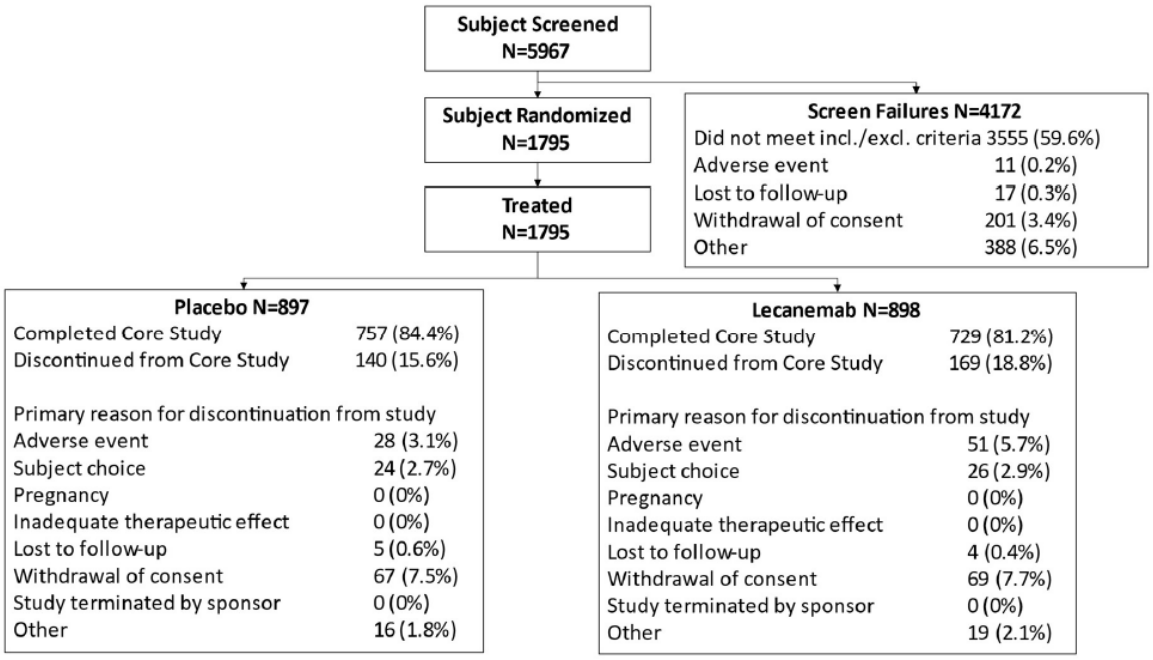
Patient Disposition

BAN2401-G000-301 was conducted between 27 Mar 2019 and 25 Aug 2022 at 235 study sites that randomized subjects in North America (112), Europe (which includes Australia, 55), Asia-Pacific (47), and China (21).

Of 5967 subjects screened for entry into the study, 4172 were screen failures and 1795 were randomized into the study. Of the 4172 screen failures, 3555 (59.6%) subjects failed to meet inclusion or exclusion criteria, 201 (3.4%) subjects withdrew consent, and 388 (6.5%) subjects were excluded for other reasons (Figure 1).

All 1795 (100%) subjects received at least 1 dose of study drug (PBO 897 [100%]; LEC10-BW 898 [100%]). Of the 1795 subjects, 757 (84.4%) subjects receiving PBO and 729 (81.2%) subjects receiving LEC10-BW completed the Core Study. Of the subjects who discontinued the study, reasons for discontinuation were similar between PBO and LEC10-BW, with the most common reasons being withdrawal of consent and adverse event.

Figure 1 **Overall Subject Disposition in Study 301**



Subjects who completed Visit 42 are considered as subjects who completed Core Study. If subjects have

missing primary reason for discontinuation, they are counted under “Other” for discontinuation reason.

N = number of subjects in treatment group.

Note: This figure was copied from page 119 of the sponsor’s study report

Table 2 Analysis Sets for Study 301 and substudies

Analysis Set	PBO (N=897) n (%)	LEC10-BW (N=898) n (%)	Combined Total (N=1795) n (%)
Safety Analysis Set[a]	897 (100)	898 (100)	1795 (100)
Intent To Treat (Full Analysis Set+)[b]	875 (97.5)	859 (95.7)	1734 (96.6)
Intent To Treat (FDA Full Analysis Set)[c]	833 (92.9)	833 (92.8)	1666 (92.8)
Per Protocol Analysis Set[d]	799 (89.1)	730 (81.3)	1529 (85.2)
PD Analysis Set (Amyloid PET)[e]	353 (39.4)	363 (40.4)	716 (39.9)
PD Analysis Set (Tau PET)[e]	122 (13.6)	135 (15.0)	257 (14.3)
PD Analysis Set (Plasma)[e]	852 (95.0)	847 (94.3)	1699 (94.7)
PD Analysis Set (CSF)[e]	139 (15.5)	142 (15.8)	281 (15.7)
PD Analysis Set (vMRI)[e]	825 (92.0)	805 (89.6)	1630 (90.8)
PK Analysis Set (Serum)[f]	1 (0.1)	893 (99.4)	894 (49.8)
PK Analysis Set (CSF)[f]	1 (0.1)	137 (15.3)	138 (7.7)

Percentages are based on the number of randomized subjects in the relevant treatment group.
COVID-19 = coronavirus disease of 2019, CSF = cerebrospinal fluid, PET = positron emission tomography, PD = pharmacodynamic, PK = pharmacokinetic, vMRI = volumetric magnetic resonance imaging.
a: The Safety Analysis Set is the group of all allocated subjects who received at least one dose of study drug.
b: The Intent To Treat (Full Analysis Set+) is the group of randomized subjects who received at least one dose of study drug who have a baseline assessment and at least one postdose primary efficacy measurement.
c: The Intent To Treat (FDA Full Analysis Set) is the group of randomized subjects who received at least one dose of study drug, who have a baseline assessment and at least one postdose primary efficacy measurement, and who are not randomized on or before the end date of dosing hold at the sites which have dosing hold with 6 or more weeks (≥42 days, which equal to 3 consecutive doses) during COVID-19 period of 01 March to 31 July 2020.
d: The Per Protocol Analysis Set is the subset of subjects in the ITT FDA FAS who sufficiently complied with the protocol.
e: The PD Analysis Set is the group of subjects who received at least one dose of study drug, and who have sufficient PD data to derive at least one PD parameter (have baseline and at least one postdose assessment).
f: The PK Analysis Set is the group of subjects with at least one quantifiable lecanemab serum concentration (analysis set for serum) or CSF concentration (analysis set for CSF) with a documented dosing history.

Note: This table was copied from page 121 of the sponsor’s study report

Table 3 summarizes study 301 subject disposition and important intercurrent events.

Table 3 Study 301 Subject Disposition and Intercurrent Events

	Placebo	Lecanemab 10 mg/kg biweekly
Randomized	**897**	**898**
FAS+	**875**	**859**
FDA FAS	**833**	**833**
Symptomatic Alzheimer's medication changes	**101 (11.2%)**	**96 (10.7%)**
Deaths within 79 Weeks	**8**	**7**
Missing Week 79 CDR-SB assessment	**140 (15.6%)**	**184 (20.5%)**

Baseline Demographics

Demographic and other baseline characteristics of the randomized subjects are presented in Table 4. This study made efforts to enhance global enrollment of a racially and ethnically diverse group of subjects. Of the 1795 subjects in the global population, 938 (52.3%) were female, 1381 (76.9%) White, 303 (16.9%) Asian (with the breakdown of 8.5% Japanese, 7.2% South Korean, and 0.7% Chinese), 47 (2.6%) were Black. Of the 947 subjects in the United States (US), 895 (94.5%) were White, 7 (0.7%) Asian, and 43 (4.5%) Black, and for ethnicity, 213 (22.5%) were Hispanic. Overall median age was 72.0 (range: 50 to 90) years.

Table 4 Baseline Demographics in Study 301

Category	PBO (N = 897)	LEC10-BW (N = 898)	Combined Total (N = 1795)
Age (year)[a]			
n	897	898	1795
Mean (SD)	71.1 (7.79)	71.4 (7.88)	71.3 (7.83)
Min, Max	50, 90	50, 90	50, 90
Sex, n (%)			
Male	421 (46.9)	436 (48.6)	857 (47.7)
Female	476 (53.1)	462 (51.4)	938 (52.3)
Race, n (%)			
White	696 (77.6)	685 (76.3)	1381 (76.9)
Black or African American	25 (2.8)	22 (2.4)	47 (2.6)
Asian	150 (16.7)	153 (17.0)	303 (16.9)
American Indian or Alaskan Native	2 (0.2)	0	2 (0.1)
Native Hawaiian or Other Pacific Islander	0	1 (0.1)	1 (0.1)
Other	12 (1.3)	21 (2.3)	33 (1.8)
Missing	12 (1.3)	16 (1.8)	28 (1.6)
APOE4 carrier status (Laboratory), n (%)			
Carriers	611 (68.1)	620 (69.0)	1231 (68.6)
Heterozygous	478 (53.3)	479 (53.3)	957 (53.3)
Homozygous	133 (14.8)	141 (15.7)	274 (15.3)
Noncarriers	286 (31.9)	278 (31.0)	564 (31.4)
Use of AD symptomatic medication at baseline (CRF), n (%)			
Yes	477 (53.2)	466 (51.9)	943 (52.5)
No	420 (46.8)	432 (48.1)	852 (47.5)
Clinical subgroup (CRF), n (%)			
MCI due to AD	555 (61.9)	552 (61.5)	1107 (61.7)
Mild AD dementia	342 (38.1)	346 (38.5)	688 (38.3)
Number of years of disease since diagnosis			
n	895	898	1793
Missing	2	0	2
Mean (SD)	1.34 (1.538)	1.43 (1.527)	1.38 (1.533)
Median	0.80	0.80	0.80
Min, Max	0, 11.2	0, 10	0, 11.2
Number of years since onset of symptoms			
n	897	897	1794
Missing	0	1	1
Mean (SD)	4.15 (2.518)	4.14 (2.354)	4.15 (2.437)
Median	3.60	3.80	3.70
Min, Max	0.5, 25.6	0.4, 21.2	0.4, 25.6
Age at onset of symptoms (Years)			
n	897	897	1794
Missing	0	1	1
Mean (SD)	67.6 (8.04)	68.0 (8.08)	67.8 (8.06)
Median	68.3	68.8	68.6
Min, Max	29.9, 86.9	38, 85.7	29.9, 86.9

Percentages are based on the total number of subjects in relevant treatment group.
AD = Alzheimer's disease, APOE4 = apolipoprotein E4, CRF = case report form, IxRS = interactive voice and web response system, MCI = mild cognitive impairment, Min = minimum, Max = maximum.
a: Age is calculated at Date of Informed Consent.

Note: This table was copied from page 123 of the sponsor's study report

The mean Baseline value (and SD) for CDR-SB was 3.22 (1.336) for PBO and 3.18 (1.344) for LEC10-BW, consistent with Early Alzheimer's Disease. Baseline values for key secondary outcomes were consistent between PBO and LEC10-BW:
ADAS-Cog14 were 24.36 (7.569) and 24.42 (7.108), ADCOMS were 0.400 (0.1463) and 0.398 (0.1476), ADCS MCI-ADL were 40.9 (6.89) and 41.2 (6.68) (note: 111 patients had missing ADCS MCI-ADL scores), modified iADRS were 106.49 (11.714) and 106.84 (11.227), and MMSE were 25.6 (2.22) and 25.5 (2.19)).

3.2.1.4 Results and Conclusions

3.2.1.4.1 Applicant's Results

Overall, 57.5% of subjects received a concomitant AD symptomatic medication. The use of concomitant AD symptomatic medication was similar between PBO (519 [57.9%]) and LEC10-BW (514 [57.2%]).
In the overall population, 5.7% of subjects were on an AD symptomatic medication but did not remain on a stable dose during the study with similar rates seen for PBO (6.2%) and LEC10-BW (5.2%). In the overall population, 7.3% of subjects started a new AD symptomatic medication regardless of use at Baseline, which was similar in PBO (7.5%) and LEC10-BW (7.1%).

The study met the primary objective. LEC10-BW treatment resulted in highly statistically significant results on the primary endpoint of change from baseline in CDR-SB at 18 months. The primary analysis was the adjusted mean difference of the change from baseline in CDR-SB at 18 months between PBO and LEC10-BW on ITT FAS+.
There was a highly statistically significant difference between PBO and LEC10-BW on change from baseline of CDR-SB at 18 months, with an adjusted mean treatment difference of -0.451, 27.1% less decline with LEC10-BW compared to PBO, P=0.00005 (Table 5 and Figure 2). Starting as early as 6 months and across all subsequent time points, LEC10-BW showed highly statistically significant changes in CDR-SB from baseline compared to PBO (all P<0.01). The absolute treatment difference increases over time within the study as can be seen in Figure 2.

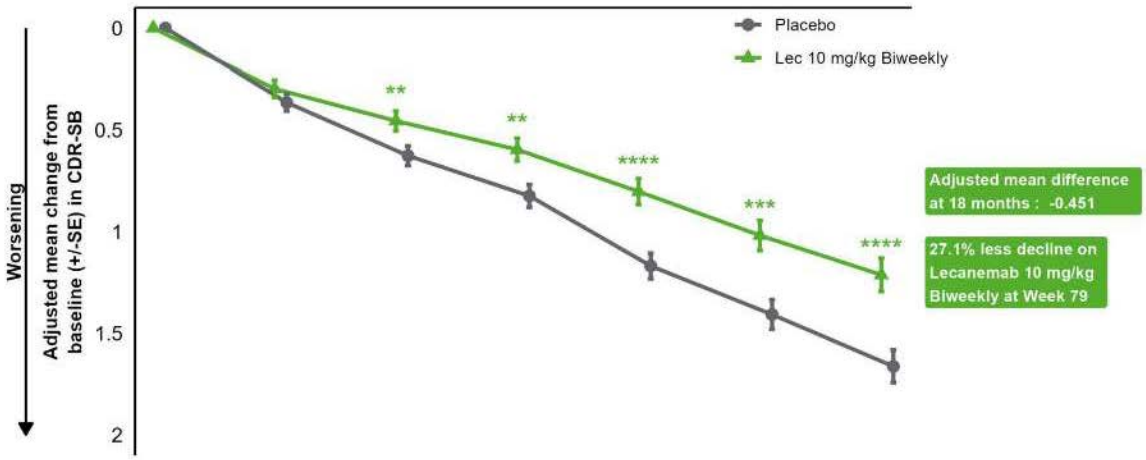
Table 5 Change from Baseline in CDR-SB Score at 18 Months – MMRM – Core Study – Intent to Treat (Full Analysis Set+)

Parameter Visit Statistic	PBO (N = 875)	LEC10-BW (N = 859)
CDR-SB		
Week 79		
m	875	859
n	757	714
Adjusted mean (SE)	1.663 (0.080)	1.213 (0.082)
Adjusted mean difference: Lecanemab - Placebo		-0.451
95% Confidence interval for differences		-0.669, -0.233
P-value		0.00005
% Difference vs. Placebo		-27.1%

m shows the number of subjects who are included in MMRM, n shows the number of subjects at each visit. The change from baseline for overall population is analyzed using the MMRM with treatment group, visit, treatment group by visit interaction, clinical subgroup, use of AD symptomatic medication at baseline, *APOE4* carrier status, region, baseline value by visit interaction as fixed effects, and baseline value as covariate. Missing values are not imputed and assumed to be missing at random. % difference is calculated as adjusted mean difference divided by adjusted mean for placebo group.
AD = Alzheimer's disease, *APOE4* = apolipoprotein E4, CDR-SB = Clinical Dementia Rating – Sum of Boxes, m = number of subjects included in the MMRM, MMRM = mixed model for repeated measures, N = number of subjects in treatment group.

Note: This table was copied from page 127 of sponsor's study report

Figure 2 Plot of Adjusted Mean Change (±SE) from Baseline in CDR-SB –Core Study – (Full Analysis Set+)



	Baseline	Week 13	Week 27	Week 39	Week 53	Week 65	Week 79
Placebo	875	849	828	813	779	767	757
Lec 10 mg/kg Biweekly	859	824	798	779	765	738	714

Note: This figure was copied from page 128 of the sponsor's study report

In the FAS analysis set for FDA with prespecified exclusions of sites due to COVID pandemic the results were as follows.
At week 78 sample sizes non-missing were 719 and 693
Adjusted mean (SE) were 1.603 (0.081) and 1.208 (0.082)
Adjusted mean difference: Lecanemab - Placebo -0.394
95% Confidence interval for differences: -0.613, -0.176
P-value: 0.00040
% Difference vs. Placebo: -24.6%

Table 6 Statistical Analysis of Change from Baseline in CDR-SB by Visit – MMRM Core Study Intent To Treat (FDA Full Analysis Set)

Parameter Visit Statistic	Placebo (N = 833)	Lecanemab 10 mg/kg Biweekly (N = 833)
CDR-SB		
Week 79		
m	833	833
n	719	693
Adjusted mean (SE)	1.603 (0.081)	1.208 (0.082)
Adjusted mean difference: Lecanemab - Placebo		-0.394
95% Confidence interval for differences		-0.613, -0.176
P-value		0.00040
% Difference vs. Placebo		-24.6%

Source: Listing 16.2.6.1
CDR-SB = Clinical Dementia Rating - Sum of Boxes, MMRM = mixed model for repeated measures.
m shows the number of subjects who are included in MMRM and is the same across all visits. n shows the number of subjects at each visit and may be different from visit to visit.
The change from baseline for overall population is analyzed using the MMRM with treatment group, visit, treatment group by visit interaction, clinical subgroup, use of AD symptomatic medication at baseline, APOE4 carrier status, region, baseline value by visit interaction as fixed effects, and baseline value as covariate. Missing values are not imputed and assumed to be missing at random. The MMRM for each subgroup is similar and is reduced by removing corresponding subgroup from the model for overall population.
% difference is calculated as adjusted mean difference divided by adjusted mean for placebo group.

Note: Table was copied from page 1058 of the sponsor's study report

CHANGE FROM BASELINE IN AMYLOID PET USING CENTILOIDS AT 18 MONTHS FOR BRAIN AMYLOID LEVELS

Centiloid values are presented by combining data across all tracers. The extent of amyloid reduction is dependent on baseline amyloid levels.

In this clinical study, the baseline level was 77.9 Centiloids, and at the end of the study, the level was 23.0 in LEC10-BW, which is below the threshold for amyloid negativity of approximately 30 Centiloids.

In the PET substudy (for MMRM analysis: PBO 344 subjects; LEC10-BW 354 subjects), treatment with LEC10-BW reduced amyloid plaque burden at all timepoints, starting at 3 months (P<0.001). At 18 months of treatment, LEC10-BW demonstrated a statistically significant reduction in amyloid PET using Centiloids compared to PBO. Adjusted mean change in Centiloids at 18 months was -55.5 and 3.6 for LEC10-BW and PBO, respectively (adjusted mean treatment difference: -59.1; P<0.00001). The absolute treatment difference increases over time.

CHANGE FROM BASELINE IN ADAS-COG14 AT 18 MONTHS

There was a highly statistically significant difference between PBO and LEC10-BW on change from baseline of ADAS-Cog14 at 18 months, with an adjusted mean treatment difference of -1.442, and 25.8% less decline with LEC10-BW compared to PBO, P=0.00065 .

CHANGE FROM BASELINE IN ADCOMS AT 18 MONTHS

There was a highly statistically significant difference between PBO and LEC10-BW on change from baseline of ADCOMS at 18 months, with an adjusted mean treatment difference of -0.050, and 23.5% less decline with LEC10-BW compared to PBO, P=0.00002. Starting as early as 6 months (P<0.05) and across all subsequent time points, LEC10-BW showed highly

statistically significant changes in ADCOMS from baseline compared to PBO (all P<0.001). The absolute treatment difference increases over time.

CHANGE FROM BASELINE IN ADCS MCI-ADL
There was a highly statistically significant difference between PBO and LEC10-BW on change from baseline of ADCS MCI-ADL at 18 months, with an adjusted mean treatment difference of 2.016, 36.6% less decline with LEC10-BW compared to PBO, P<0.00001.

The key secondary endpoint results are summarized in Table 7.

Table 7 Hierarchy of Key Secondary Endpoint Results at Week 79 in FAS+ population

Endpoint	Treatment Group	N	Baseline score	Week 79 LS Mean	PBO-LEC Difference (95% C.I.)	p-value
Amyloid PET (Centiloids)	Placebo	325	1.4	3.6	59.2 (55.6, 62.7)	<.0001
	Lecanemab	342	1.4	-55.5	--	
ADAS-COG-14	Placebo	872	24.4	5.6	1.4 (0.6, 2.3)	0.0007
	Lecanemab	854	24.4	4.2	--	
ADCOMS (x 100)	Placebo	833	39.9	20.9	4.5 (2.2, 6.9)	0.0002
	Lecanemab	831	39.7	16.3	--	
ADCS-ADL-MCI	Placebo	796	41.1	-5.5	-2.0 (-2.8, -1.2)	<.0001
	Lecanemab	783	41.3	-3.5	--	

3.2.1.4.2 Reviewer's Results

Twenty two (2.5%) placebo and 39 (4.3%) lecanemab had no post-baseline efficacy assessments and were therefore not in the FAS+ (or FAS agreed with FDA population on which the primary analysis was based). There were 8 placebo and 7 lecanemab deaths in the ITT population by Week 79, of which 5 and 7, respectively, were in the FAS+ population. Ignoring these bad outcomes in the primary analysis could potentially cause bias in the primary analysis, but the proportion of deaths is low enough for any corresponding bias to be small. Tipping point sensitivity analyses for missing data based on multiple imputations using shift parameters (delta)

for informative missingness, separately for each treatment group for generating outcomes for missing data were performed.

The robustness of the primary analysis outcomes was evaluated based on the scientific plausibility of the tipping point. The applicant reported a tipping point of 1.5 for the FAS+ population, meaning missing outcomes would have to have a 1.5 point worse shift on CDR-SB for lecanemab than the shift for placebo missing outcomes in order for the primary analysis to lose significance, assuming no informative missingness for placebo. The sponsor used half point increments for the shift parameter. If smaller shifts are considered the tipping point is closer to 1 than 1.5, being about 1.1. The tipping point is lower if data after both ARIA-E and/or changes in concomitant AD medications are censored. In the overall population, 5.7% of subjects were on an AD symptomatic medication but did not remain on a stable dose during the study with similar rates seen for PBO (6.2%) and LEC10-BW (5.2%). In the overall population, 7.3% of subjects started a new AD symptomatic medication regardless of use at Baseline, which was similar in PBO (7.5%) and LEC10-BW (7.1%). If data after both ARIA-E and/or changes in concomitant AD medications are censored there is 39.5% missing at Week 79 for lecanemab and 28.2% for placebo and the tipping point for the primary analysis of CDR-SB is 0.5 meaning under the assumption that missing or censored lecanemab Week 79 outcomes would be 0.5 worse on CDR-SB than observed data in the lecanemab group for patients who had no ARIA or changes in concomitant AD medications with the same covariates as the affected subject.

It is notable that the proportion of missing data at Week 79 was higher for the key secondary ADCS-ADL-MCI endpoint than for the CDR-SB endpoint: 796 (88.7%) placebo and 783 (87.2%) lecanemab subjects were included (having at least one post-baseline efficacy assessment) in the ADCS-ADL-MCI analysis.

Table 8 Statistical Analysis of Change from Baseline in CDR-SB by Visit Censoring by Treatment Discontinuation or AD treatment Initiation/Dose Adjustment - MMRM

Overall

Parameter Visit Statistic	Placebo (N = 833)	Lecanemab 10 mg/kg Biweekly (N = 833)
CDR-SB		
Week 79		
m	803	785
n	614	579
Adjusted mean (SE)	1.478 (0.080)	1.125 (0.081)
Adjusted mean difference: Lecanemab - Placebo		-0.353
95% Confidence interval for differences		-0.568, -0.138
P-value		0.00132
% Difference vs. Placebo		-23.9%

Source: Listing 16.2.6.1
CDR-SB = Clinical Dementia Rating - Sum of Boxes, MMRM = mixed model for repeated measures.
m shows the number of subjects who are included in MMRM and is the same across all visits. n shows the number of subjects at each visit and may be different from visit to visit.
The change from baseline for overall population is analyzed using the MMRM with treatment group, visit, treatment group by visit interaction, clinical subgroup, use of AD symptomatic medication at baseline, APOE4 carrier status, region, baseline value by visit interaction as fixed effects, and baseline value as covariate. Missing values are not imputed and assumed to be missing at random.
% difference is calculated as adjusted mean difference divided by adjusted mean for placebo group.

Note: This table was copied from page 1241 of the sponsor's study report

Overall, the incidence of TEAEs considered by the investigator to be related to study drug was lower in PBO (197 [22.0%]) than LEC10-BW (401 [44.7%]). The most commonly reported (≥2%) treatment-related TEAEs were (Table 14.3.1.5.2):

- Infusion-related reaction (PBO 64/897 [7.1%]; LEC10-BW 234/898 [26.1%])
- ARIA-H (PBO 67/897 [7.5%]; LEC10-BW 122/898 [13.6%])
- ARIA-E (PBO 15/897 [1.7%]; LEC10-BW 113/898 [12.6%])
- Superficial siderosis of central nervous system (PBO 20/897 [2.2%]; LEC10-BW 47/898 [5.2%]).

Occurrences of ARIA may have risked unblinding of subjects and investigators. However, such bias was minimized by the study design and conduct which masked clinical raters to safety assessments. Table 9 shows the prespecified sensitivity analysis censoring CDR-SB after occurrence of ARIA-E. Note that conclusions based on this analysis must be limited because censoring data after a post-baseline event that occurred more in one group than the other, could cause confounding.

Table 9 Statistical Analysis of Change from Baseline in CDR-SB by Visit Censoring by Occurrence of First Treatment-Emergent ARIA-E

Overall

Parameter Visit Statistic	Placebo (N = 833)	Lecanemab 10 mg/kg Biweekly (N = 833)
CDR-SB		
Week 79		
m	797	724
n	650	546
Adjusted mean (SE)	1.624 (0.082)	1.140 (0.087)
Adjusted mean difference: Lecanemab - Placebo		-0.484
95% Confidence interval for differences		-0.712, -0.256
P-value		0.00003
% Difference vs. Placebo		-29.8%

Source: Listing 16.2.6.1
ARIA = amyloid-related imaging abnormalities, CDR-SB = Clinical Dementia Rating - Sum of Boxes, MMRM = mixed model for repeated measures.
m shows the number of subjects who are included in MMRM and is the same across all visits. n shows the number of subjects at each visit and may be different from visit to visit.
The change from baseline for overall population is analyzed using the MMRM with treatment group, visit, treatment group by visit interaction, clinical subgroup, use of AD symptomatic medication at baseline, APOE4 carrier status, region, baseline value by visit interaction as fixed effects, and baseline value as covariate. Missing values are not imputed and assumed to be missing at random.
% difference is calculated as adjusted mean difference divided by adjusted mean for placebo group.
Subject's data on or after occurrence of first ARIA is not included.

Note: This table was copied from page 1247 of the sponsor's study report

Subject level correlation between clinical changes on CDR-SB and change in amyloid PET using Centiloids and amyloid PET SUVR composite for brain amyloid levels was listed as a biomarker endpoint in the statistical analysis plan. The applicant reported that the Pearson correlation between Change from baseline in amyloid PET using Centiloids at Week 13 and change from

baseline in CDR-SB at Week 79 in the lecanemab arm in the pet substudy (N=246) was -0.068 (p=0.2851). Partial Pearson correlation, i.e., correlation adjusted for baseline Amyloid PET and baseline CDR-SB was 0.069 p=0.2801 (Table 10).

Table 10 Correlation Analysis for Change from Baseline Between Amyloid PET using Centiloids and Clinical Endpoints (CDR-SB, ADAS-Cog14,

Pairs Statistic	Placebo (N = 351)	Lecanemab 10 mg/kg Biweekly (N = 362)	Combined Total (N = 713)
Change from baseline in amyloid PET using Centiloids at Week 13 and change from baseline in CDR-SB at Week 79			
n	247	246	493
Pearson correlation	-0.056	-0.068	-0.025
P-value	0.37809	0.28508	0.57594
Spearman correlation	-0.030	-0.184	-0.076
P-value	0.63436	0.00379	0.09246
Partial Pearson correlation	-0.035	0.069	0.069
P-value	0.58819	0.28008	0.12465
Partial Spearman correlation	0.019	0.035	0.058
P-value	0.76246	0.58403	0.20240

Note: This table was copied from page 4198 of the sponsor's study report

3.3 Evaluation of Safety

Safety in general is not addressed in this review. Please see the Clinical safety review.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, and Geographic Region

4.1.1 Gender, Race, and Age

Gender

Fifty two percent of the FAS+ population were female and 48% were male. Table 11 shows the Week 79 difference on CDR-SB in the FAS+ population by Gender subgroup.

Table 11 Primary Endpoint Difference by Gender in FAS+ population

Gender	Estimate	StdErr	Lower 95% CI limit	Upper 95% CI limit
Female	0.1915	0.1538	-0.1101	0.4931
Male	0.7258	0.1605	0.4110	1.0406

The difference between treatment effects at Week 79 on CDR-SB in males and females was nominally significant, p=0.016, with numerically less effect in females, although the estimated effect in females was still numerically better than placebo.

Age

Percentages in each age group were 20% for < 65, 43% for 65-75 and 37% for > 75. Table 12 shows the Week 79 difference on CDR-SB in the FAS+ population by Age subgroup.

Table 12 Primary Endpoint Difference by Age Group in FAS+ population

AGE GROUP	Estimate	StdErr	Lower 95% CI limit	Upper 95% CI limit
<65 years	0.1320	0.2466	-0.3517	0.6156
>=65 and <75 years	0.3700	0.1686	0.03940	0.7007
>=75 years	0.7300	0.1854	0.3664	1.0936

Race

Percentages by race were 77% for White, 17% for Asian, and 6% were Other. Table 13 shows the Week 79 difference on CDR-SB in the FAS+ population by Race subgroup.

Table 13 Primary Endpoint Difference by Race at Week 79 FAS+ population

Race	Estimate	Stderr	Lower 95% CI limit	Upper 95% CI limit
Asia-Pacific	0.3478	0.2626	-0.1673	0.8629
Other	0.1603	0.4465	-0.7156	1.0362
White	0.4926	0.1277	0.2420	0.7431

4.1.2 Geographic Region

The region effect variable for the primary analysis model and also the stratification factor had 3 categories: Europe, Asia-Pacific, and North America. Region and Region by Visit effects were nominally significant p<0.0001 indicating that CDR-SB scores were significantly variable by region, with some variation in the pattern across visits by region. Table 14 shows estimated differences on the CDR-SB at Week 79 by Region subgroup in the FAS+ population.

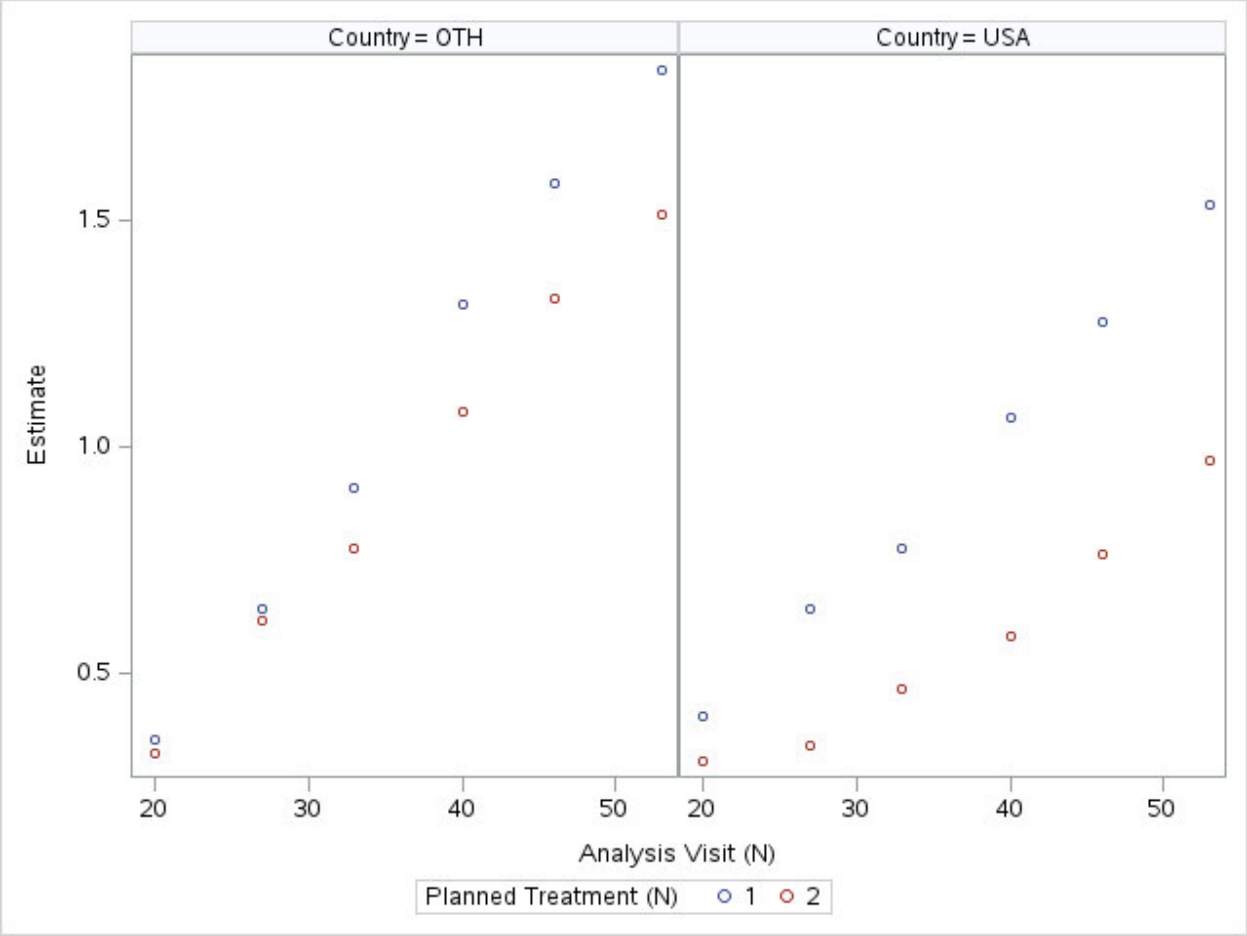
Table 14 Primary Endpoint Difference by Region in FAS+ population

Region	Estimate	StdErr	Lower 95% CI limit	Upper 95% CI limit
Asia-Pacific	0.3360	0.2632	-0.1802	0.8523
Europe	0.3507	0.2227	-0.08619	0.7875
North America	0.5145	0.1449	0.2303	0.7988

There was also considerable variation in CDR-SB, including estimated Week 79 treatment effects, across countries. Country, country by visit, and treatment by country effects had exploratory p-values of <.0001, <.0001, and 0.0718, respectively. For example, Italy (N=72) favored placebo numerically with an estimated lecanemab-placebo Week 79 CDR-SB difference +0.95 95% C.I.=(- 0.08, 1.98) p=0.07 in the FDA FAS population. Note that the randomization was not stratified by country, but by region.

The observed treatment effect on CDR-SB at Week 79 was larger in the US, which accounted for 52% of the FAS+ population, than outside the US. Figure 3 shows the differences in progression patterns by group within the US and outside the US in the FAS+ population.

Figure 3 LS Means for Primary Endpoint over Visits and Region(US vs. non-US) in FAS+ population



Note: In the figure Planned Treatment =1 for placebo and 2 for lecanemab

4.1.2.1 Individual Sites

There do not appear to be any highly influential sites for efficacy in terms of the primary endpoint, CDR-SB, e.g., exclusion of no single site would overturn the significance of the primary analysis result.

4.2 Other Special/Subgroup Populations

A smaller treatment effect on the primary endpoint, CDR-SB, at Week 79 was observed in APOE4 homozygotes (N=268 in FAS+ population), a prespecified subgroup for analysis. Note that the randomization was stratified by APOE4 carrier/non-carrier and the carrier stratum includes both heterozygotes and homozygotes. The effect was numerically worse than placebo in this subgroup for CDR-SB at Week 79, lecanemab-placebo=0.25 (S.E.=0.28) [95% C.I.=- 0.30, 0.80], p=0.367. There was a nominally significant quantitative interaction (p=0.017) between treatment group and APOE4 genotype in a subgroup analysis but it did not reach the level of a

qualitative interaction (e.g., a subgroup statistically significant in the opposite direction to the overall result). For the key secondary endpoints ADAS-COG-14 and ADCS-MCI-ADL the treatment difference was still smaller in the homozygotes than in APOE4 non-carriers and heterozygotes, but unlike for CDR-SB it was numerically better than placebo for these key secondary endpoints. Therefore, across the primary and key secondary endpoints there was a common pattern of a smaller effect in homozygotes, but no compelling evidence that it is worse than placebo.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

A smaller treatment effect on the primary endpoint was observed for APOE4 homozygotes. The trend in the wrong direction on the primary endpoint did not reach the level of a qualitative interaction and trended in the right direction, favoring lecanemab numerically, for key secondary endpoints. Thus, there is insufficient evidence of a qualitative interaction but a quantitative interaction, i.e., a smaller effect but still favoring the drug may be plausible in this subgroup. For example, a larger effect was expected in APOE4 carriers than non-carriers, based on study 201 results and results for other amyloid reducing investigational therapies, but a larger effect was seen in non-carriers than carriers or even APOE4 heterozygote carriers in study 301. This also supports possible differential effects by APOE4 genotype.

There was 16% missing data in placebo and 21% in lecanemab for the primary endpoint at Week 79 (including 2.5% of placebo and 4.3% of lecanemab with no post-baseline CDR-SB assessments). However, the results appear reasonably robust to missing data based on tipping point analysis and other sensitivity analyses.

On the basis of a secondary analysis model assuming linearity over time of CDRSB for each subject (with random subject intercepts and slopes) the applicant claims that the differences on CDRSB suggest the preservation of approximately 5.3 months relative to PBO at 18 months. However, the assumption of linearity over time on which this time estimate relies for validity appears questionable since a quadratic model over time for each subject has a smaller Akaikes' information criterion which is better (28144.4 for quadratic vs 28232.2 for linear), a measure of model fit with a penalty for model complexity, than the linear model. Furthermore, this time estimate may be unreliable because it is not directly measured, i.e., the time preservation is not the dependent variable, and as such the time estimate will vary depending on the chosen dependent variable (e.g., CDRSB, ADAS-cog-14, ADCS-MCI-ADL). It would also be important for proper context to consider the standard error or uncertainty of the time estimate. However, this was not provided by the applicant; the standard error of the estimated time preservation is not easily obtainable because time preservation is not directly measurable and it was not the dependent variable in the analysis. Therefore, this time preservation estimate should not be overinterpreted or emphasized without considering these limitations.

5.2 Collective Evidence

Collective evidence is not considered in this review since there was only one phase 3 double-blind, controlled trial and a Bayesian adaptive dose finding phase 2 study.

5.3 Conclusions and Recommendations

At the Type B BTD Multidisciplinary meeting held on 10 Sep 2021, the FDA agreed that the proposed biomarker and data efficacy from Study 201
Core and OLE Phase could support a Biologics License Application (BLA) submission for lecanemab under the accelerated approval pathway and that Study 301 could serve as the confirmatory study to verify the clinical benefit of lecanemab.

In January 2023, Lecanemab received accelerated approval based on the effect on amyloid in study 201.

Based on highly significant results on the primary endpoint, CDR-SB, at Week 79 as well as multiplicity controlled key secondary endpoints, Study 301 appears to confirm the clinical benefit of lecanemab in early AD.

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/

TRISTAN S MASSIE
06/29/2023 06:08:59 PM

JOHN P LAWRENCE
07/01/2023 06:51:33 AM

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07/02/2023 02:18:20 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761269Orig1s001

CLINICAL PHARMACOLOGY REVIEW(S)

Office of Clinical Pharmacology Review

NDA or BLA Number	761269-S001
Link to EDR	\\CDSESUB1\evsprod\BLA761269\0120
Submission Date	01/06/2023
Submission Type	Efficacy Supplement, priority review
Brand Name	LEQEMBI™
Generic Name	Lecanemab-irmb
Dosage Form and Strength	100 mg/mL solution in a single-dose vial • 500 mg/5 mL • 200 mg/2 mL
Route of Administration	Intravenous infusion
Proposed Indication	Treatment of Alzheimer's Disease
Proposed Dose/Regimen	10 mg/kg administered as an intravenous infusion over approximately one hour, once every two weeks
Applicant	Eisai Inc.
Associated IND	IND 105081
OCP Review Team	Yifei Zhang*, Ph.D., Vishnu Sharma*, Ph.D., Mohsen Rajabiabhari*, Ph.D., Xiulian Du*, Ph.D., Hobart Rogers*, Ph.D., Atul Bhattaram#, Ph.D., Yow-Ming Wang#, Ph.D., Jeffrey Kraft#, Ph.D., Bilal AbuAsal#, Ph.D., Sreedharan Sabarinath^, Ph.D., Ramana Uppoor^, Ph.D., Hao Zhu^, Ph.D.
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1. EXECUTIVE SUMMARY

LEQEMBI (Lecanemab-irmb, BAN2401) is a humanized immunoglobulin gamma 1 (IgG1) monoclonal antibody (mAb) directed against aggregated soluble and insoluble forms of amyloid beta (Aβ). LEQEMBI was approved by FDA for the treatment of Alzheimer's Disease (AD) under the accelerated approval pathway on January 6, 2023, based on reduction in amyloid beta plaques observed in the Phase 2 study BAN2401-G000-201 (Study 201). The recommended dosing regimen is an intravenous infusion of 10 mg/kg lecanemab over approximately one hour, administered once every two weeks.

In the current efficacy supplement, the Applicant is requesting the traditional approval of LEQEMBI with the same indication and dosing regimen. Study BAN2401-G000-301 (Study 301) is the confirmatory study to verify the clinical benefit of lecanemab. Study 301 Core was a 1795-subject, multicenter, double-blind, placebo-controlled study to demonstrate the superiority of lecanemab 10 mg/kg biweekly versus placebo, followed by an open-label extension (OLE) Phase. In Study 301 Core, lecanemab treatment showed significant results on primary endpoint (Clinical Dementia Rating - Sum of Boxes [CDR-SB]) and all key secondary endpoints. There was a statistically significant difference between placebo and lecanemab 10 mg/kg bi-weekly IV infusion on change from baseline of CDR-SB at 18 months, demonstrating slowing of disease progression, with an adjusted mean treatment difference of -0.451 (27.1% less decline with lecanemab compared to placebo, P=0.00005).

In addition to slowing of clinical decline, the effectiveness of lecanemab is supported by the changes in brain amyloid PET Centiloid and plasma/CSF biomarkers, representing effects on the underlying pathophysiology. Lecanemab reduced amyloid beta plaque in a dose- (Study 201) and time- dependent (Study 201 and Study 301) manner compared with placebo. In the Study 301 Core, treatment with lecanemab 10 mg/kg every two weeks reduced amyloid beta plaque levels in the brain, producing reductions in amyloid PET Centiloid compared to placebo at both Weeks 53 and 79 ($p<0.00001$). Meanwhile, an increase in plasma Aβ42/40 ratio and CSF Aβ[1-42], as well as a reduction in plasma p-tau181, CSF p-tau181, and CSF t-tau was observed following treatment with lecanemab compared to placebo at week 77.

The effectiveness of lecanemab is also supported by exposure-response relationships from Study 301 and Study 201. Model based exposure-response analyses for both studies demonstrated that higher exposures to lecanemab were associated with (1) greater reduction in clinical decline on CDR-SB and Alzheimer Disease Assessment Scale – Cognitive Subscale 14 (ADAS-Cog14); (2) greater reduction in amyloid beta plaque; and (3) greater increase in plasma Aβ42/40 ratio and greater reduction in plasma p-tau181. An association between reduction in amyloid beta plaque and clinical decline on CDR-SB and ADAS-Cog14 was also observed. Please refer to the clinical pharmacology review of original BLA 761269 approved on January 06, 2023 for additional details.

The review team evaluated the effect of *APOE* genotype on safety and efficacy. In Study 301 Core, the overall incidence of amyloid related imaging abnormalities - edema/effusion (ARIA-E) was lower in placebo group (1.7%) than lecanemab group (12.6%). Following lecanemab treatment, the incidence of ARIA-E was higher in *APOE* ε4 carriers (98/620 [15.8%]) than *APOE* ε4 noncarriers (15/278 [5.4%]). Of

the *APOE* ε4 carriers, the incidence of ARIA-E was lower in *APOE* ε4 heterozygotes (52/479 [10.9%]) than in *APOE* ε4 homozygotes (46/141 [32.6%]). This was consistent with the exposure-response modeling results which predicted higher ARIA-E incidence rate in *APOE* ε4 homozygotes compared to that in *APOE* ε4 heterozygotes and *APOE* ε4 noncarriers.

According to Applicant's pre-specified subgroup analysis for efficacy, the change from baseline in the clinical endpoints CDR-SB, ADAS-Cog14, and ADCS MCI-ADL (Alzheimer's Disease Cooperative Study-Activities of Daily Living Scale for Mild Cognitive Impairment) all favored lecanemab treatment compared to placebo in both *APOE* ε4 carriers and *APOE* ε4 noncarriers (randomization strata). Further subgroup analysis in *APOE* ε4 heterozygotes/homozygotes followed the similar trend across *APOE* genotypes, except for CDR-SB in *APOE* ε4 homozygotes, which favored placebo. However, fluid biomarker data in Study 301 Core suggested a consistent pattern of favoring lecanemab treatment across plasma biomarkers (Aβ42/40 ratio, p-tau181) and CSF biomarkers (Aβ[1-42], t-tau, p-tau181) for all the genotypes, including *APOE* ε4 homozygotes.

The main focus of this sBLA review was to confirm the following aspects based on data from Study 301: (1) the effectiveness of lecanemab based on slowing of disease progression, effects on brain amyloid, plasma/CSF biomarkers, and exposure-response relationships; (2) the acceptability of general dosing recommendations and the need for dose adjustment based on intrinsic factors; and (3) the effect of *APOE* genotype on efficacy and safety.

1.1 Recommendations

The Office of Clinical Pharmacology has reviewed the information in this BLA supplement and recommends approval from a clinical pharmacology perspective. Further, the review team recommends adding labeling statements regarding the benefit/risk assessment based on different genotypes. Specifically, the increased risk of ARIA in *APOE* ε4 homozygotes should be highlighted. In addition, the team recommends describing in labeling Section 14 about the subgroup findings for efficacy by *APOE* genotype, including the clinical endpoints (CDR-SB, ADAS-Cog14, ADCS MCI-ADL) and biomarkers (amyloid beta PET Centiloid, plasma Aβ42/40 ratio, plasma p-tau181).

The key review issues with specific recommendations/comments are summarized below:

Review Issue	Recommendations and Comments
Pivotal or supportive evidence of effectiveness	The pivotal evidence of effectiveness was based on the statistically significant difference on change from baseline in CDR-SB observed in Study 301 at 18 months, demonstrating the slowing of disease progression. The effectiveness of lecanemab was also supported by other endpoints in Study 301 and data from Study 201, such as the effects on brain amyloid, plasma/CSF biomarkers, and exposure-response relationships.
General dosing instructions	Intravenous infusion of 10 mg/kg lecanemab over approximately one hour, administered once every two weeks.

Dosing in patient subgroups (intrinsic and extrinsic factors)	No dose individualization is recommended based on intrinsic factors.
Labeling	Generally acceptable. The review team has specific content and formatting change recommendations.

1.2 Post-Marketing Requirements and Commitments

Not applicable.

1.3 Summary of Labeling Recommendations

The office of Clinical Pharmacology recommends the following labeling edits:

Section 12.2:

- For plasma Aβ42/40 and plasma p-tau181, move the Study 201 data from Section 14 to Section 12.2, and include Study 301 data in the table
- Describe the results of additional biomarkers: CSF Aβ [1-42], CSF p-tau181, and CSF t-tau

Section 12.3:

- Update the PK parameters (volume of distribution, clearance) based on pop-PK analysis with additional data

Section 14:

- The team recommends including a description regarding the subgroup findings by *APOE* genotype on clinical endpoints (CDR-SB, ADAS-Cog14, ADCS MCI-ADL) and biomarkers (amyloid beta PET, plasma Aβ42/40 ratio, plasma p-tau181) to inform the benefit risk assessment.

2. COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

2.1 Overview of the Product and Regulatory Background

Lecanemab, also known as BAN2401, is a humanized immunoglobulin G1 (IgG1) monoclonal antibody (mAb) directed against aggregated soluble and insoluble forms of amyloid beta. On January 6, 2023, lecanemab was approved for the treatment of Alzheimer's Disease (AD) under the accelerated approval pathway mainly based on reduction in amyloid beta plaques observed in Study 201, with additional data on efficacy endpoints and fluid biomarkers.

In the current submission, the Applicant is seeking traditional approval, with Study 301 as the confirmatory clinical trial that provides the main dataset to verify the clinical benefit of lecanemab, and Study 201 Core provides supportive data. In addition to Study 201 and Study 301, the clinical pharmacology characteristics of lecanemab have been evaluated in two Phase 1 studies (BAN2401-A001-101 and BAN2401-J081-104) as described in the original BLA761269 clinical pharmacology review. The safety of lecanemab is based on data from 8 ongoing or completed studies in 2203 lecanemab-treated subjects and 1300 placebo-treated subjects with early AD and preclinical AD.

Current therapeutic agents for patients with mild, moderate, and severe AD dementia consist of symptomatic therapies that include acetylcholinesterase inhibitors (AChEIs), such as donepezil, and the N-methyl-D-aspartate receptor antagonist, memantine. In addition, aducanumab (Aduhelm®) was approved in the US under the accelerated approval pathway in June 2021 for the treatment of AD based on a reduction in amyloid beta plaques.

2.2 General Pharmacology and Pharmacokinetic Characteristics

Serum lecanemab Cmax and AUC increased in an approximately dose-proportional manner within the assessed single dose range of 0.3 mg/kg to 15 mg/kg. The mean terminal t½ of lecanemab was 5 to 7 days when administered at 1 mg/kg or higher doses. Steady-state was achieved after 6 weeks of 10 mg/kg administered every 2 weeks, and the systemic accumulation was 1.4-fold based on AUC.

Based on the pop-PK modeling updated by including data from Study 301, the mean value (95% CI) for central volume of distribution at steady-state is 3.24 (3.18-3.30) L, and the clearance of lecanemab (95% CI) is 0.370 (0.353-0.384) L/day. Lecanemab is degraded by proteolytic enzymes and is not expected to undergo renal elimination or metabolism by hepatic enzymes. Sex, body weight, and albumin were found to impact exposure to lecanemab, however, none of these covariates were found to be clinically significant.

For additional details, please refer to the clinical pharmacology review of original BLA 761269 approved on January 06, 2023.

2.3 Clinical Pharmacology Review Questions

2.3.1 To what extent does the available clinical pharmacology information provide pivotal or supportive evidence of effectiveness?

The pivotal evidence of effectiveness for the treatment of AD is based on the statistically significant difference on change from baseline in CDR-SB following treatment with lecanemab compared to placebo, observed in Study 301 at 18 months. The results were consistent across the primary endpoint CDR-SB and all key secondary endpoints including ADAS-Cog14, ADCOMS (Alzheimer's Disease Composite Score), and ADCS MCI-ADL, and consistent with Study 201 Core. The effectiveness of lecanemab was also supported by the effects on brain amyloid and downstream fluid and imaging biomarkers and exposure-response relationships from Study 301 and Study 201.

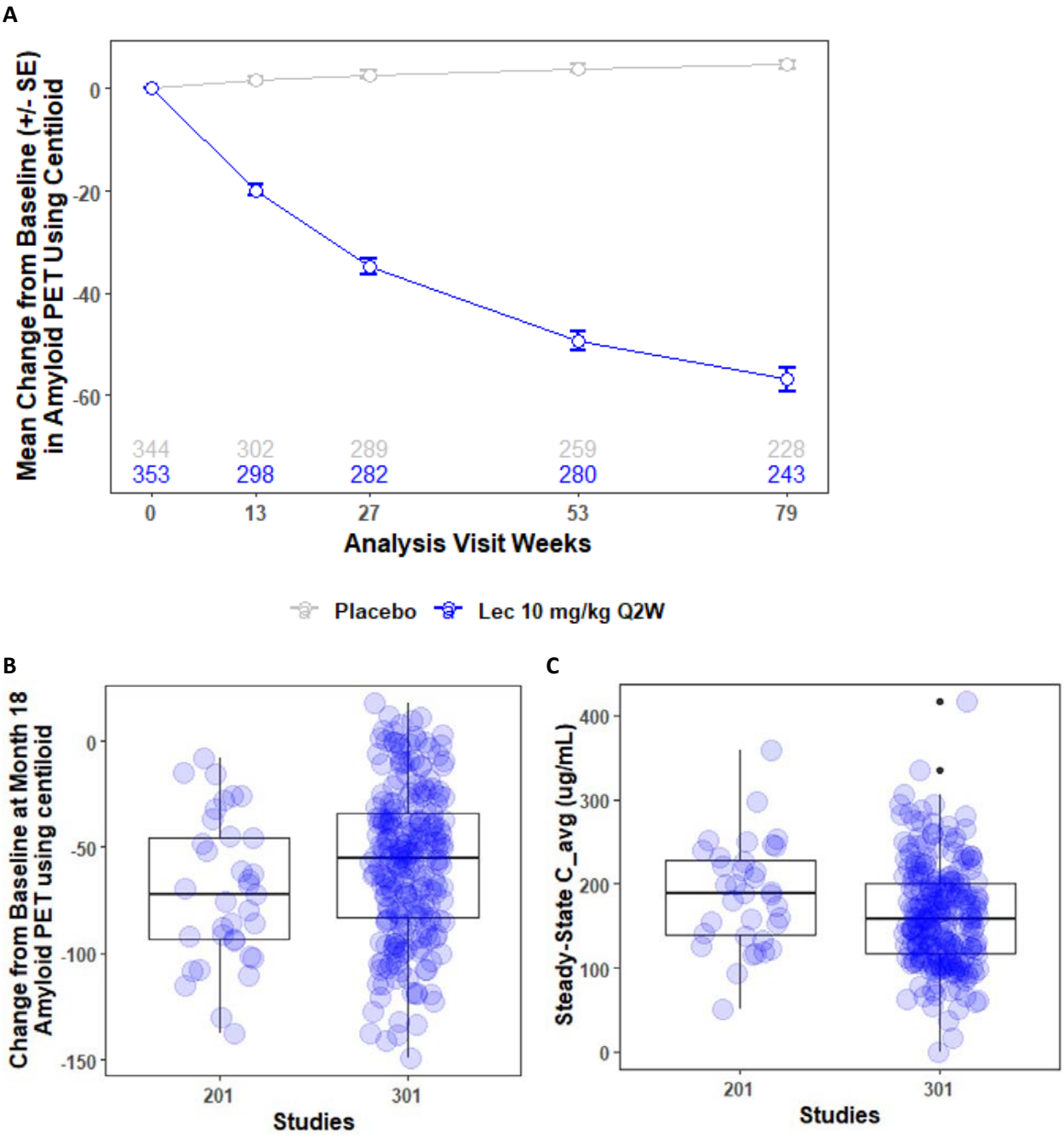
Study 301 was the confirmatory study to verify the clinical benefit of lecanemab. Study 301 was a multicenter, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of

lecanemab in patients with mild cognitive impairment (MCI) due to AD or mild AD dementia. Study 301 Core was an 18-month study in which eligible subjects were randomized in a 1:1 ratio to receive intraveneous administration of either lecanemab 10 mg/kg biweekly IV infusion or placebo, with the option to continue seamlessly in the open label extension (OLE) phase. The Study 301 Core met the primary and key secondary endpoints, with statistically significant difference between lecanemab and placebo on change from baseline of CDR-SB at 18 months, demonstrating slowing of disease progression, with an adjusted mean treatment difference of -0.451 (27.1% less decline with lecanemab compared to placebo, P=0.00005). Please refer to clinical review for additional details on efficacy assessment.

In Study 301 Core, the amyloid PET substudy showed a time-dependent reduction in amyloid PET following lecanemab treatment (**Figure 1A**). At 18 months of treatment, lecanemab treatment demonstrated statistically significant reduction in amyloid PET using Centiloids compared to placebo. The adjusted mean changes from baseline in amyloid PET using Centiloids at week 79 were 3.6 and -55.5 in placebo and lecanemab groups, respectively (adjusted mean treatment difference: -59.1; P<0.00001). The mean amyloid PET Centiloids was reduced from 77.9 at baseline to 23.0 at Week 79, which is below the threshold for amyloid positivity of approximately 30 Centiloids. Similarly, in Study 201 Core, lecanemab demonstrated significant amyloid reduction versus placebo at 12 months and 18 months of treatment with lecanemab 10 mg/kg biweekly (P<0.001, refer to original BLA 761269 clinical pharmacology review). The review team noted that the mean magnitude of amyloid reduction at Month 18 was 13 units larger in Study 201 compared to Study 301 (**Figure 1B**), possibly due to study related factors or higher PK exposures observed in Study 201 as compared to Study 301 (**Figure 1C**).

Additionally, the Applicant submitted plasma and CSF biomarker data from Study 301 to evaluate the effect of lecanemab on downstream AD pathophysiology. In Study 301, an increase in plasma Aβ42/40 ratio and CSF Aβ[1-42], as well as a reduction in plasma p-tau181, CSF p-tau181, and CSF t-tau (**Figure 2**) was observed following treatment with lecanemab compared to placebo at week 77. For these biomarkers, it should be noted that the long-term stability in bioanalytical method validations were not fully established (refer to Appendix 3.1.2). Although qualitative descriptions remain warranted, any quantitative analysis results should be interpreted with caution.

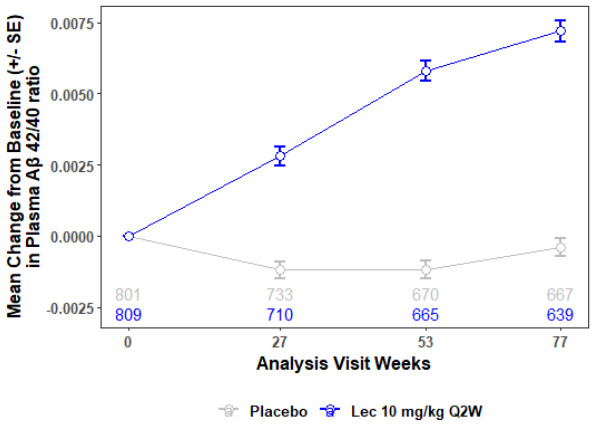
Figure 1 (A) Amyloid PET Centiloids Mean Change from Baseline over Time in Study 301; (B) Amyloid PET Centiloids at Month 18 Observed in studies 201 and 301; (C) Steady-State Average Concentrations of Lecanemab in studies 201 and 301



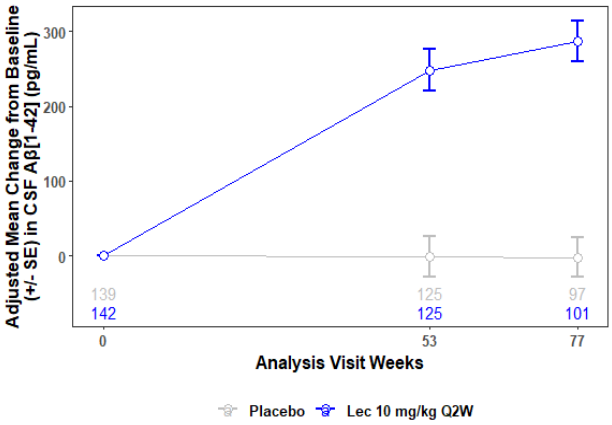
Source: Reviewer's analysis; Datasets utilized in exposure-response analysis was used for the analysis
Note: in panel B, the adjusted mean treatment difference from placebo was -72 (Study 201, n=44) and -59 (Study 301, n=354) Centiloids, respectively

Figure 2 Change from Baseline in Plasma/CSF Biomarkers over Time in Study 301

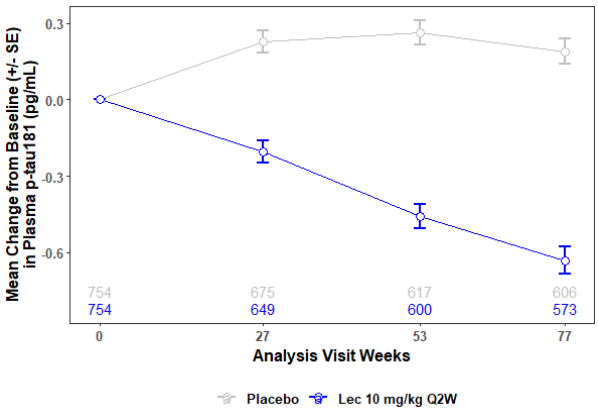
A. Plasma Aβ42/40 ratio



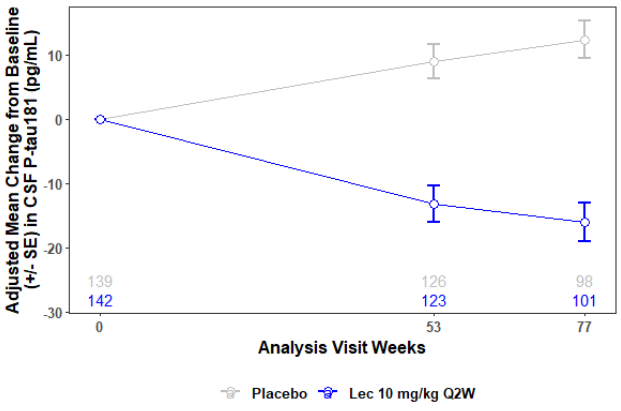
B. CSF Aβ [1-42]



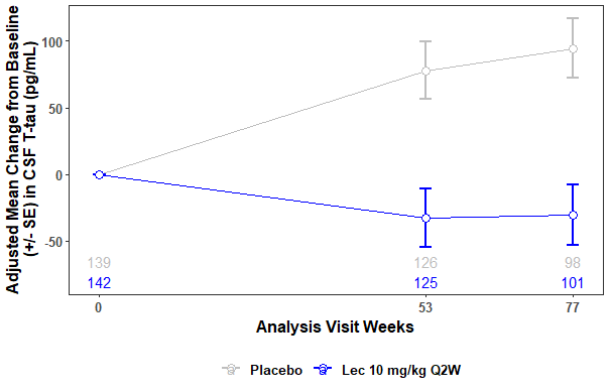
C. Plasma P-Tau181



D. CSF P-tau181



E. CSF T-Tau



Source: Reviewer's analysis; Plots A and C: Datasets utilized in exposure-response analysis was used for the analysis; Plots B, D, and E was constructed from Study 301 CSR Table 14.2.7.4.2

The Applicant also submitted data of additional biomarkers such as plasma glial fibrillary acidic protein (GFAP), CSF neurogranin, and neurofilament light chain (NfL) in plasma/CSF. Study 301 data suggested a reduction in plasma GFAP and CSF neurogranin with lecanemab treatment compared to placebo, and

literatures have been published about the association of these biomarkers with AD[1][2][3][4][5]. However, the association between treatment effect and the reduction in these biomarkers has not been firmly established across studies/dosing regimens or across different anti-amyloid products. In addition, there are limitations in bioanalytical validation (e.g., long-term stability) with the biomarkers (Appendix 3.1.2). Considering the above uncertainties, the review team recommends not to include these biomarkers in the labeling for this BLA supplement.

The effectiveness of lecanemab for the treatment of AD is also supported by the exposure-response relationships for clinical efficacy endpoints, amyloid PET Centiloids, and plasma biomarker data from studies 201 and 301. As shown in the **Figure 6** in Appendix 3.2, increase in PK exposures of lecanemab resulted in greater reduction in clinical decline on CDR-SB and ADAS-Cog14. Higher exposures to lecanemab were also associated with greater reduction in amyloid beta plaque, greater increase in plasma Aβ42/40 ratio, and greater reduction in plasma p-tau181 (**Figure 7** and **Figure 8** in Appendix 3.2). Reductions in amyloid beta plaque are associated with reduction in clinical decline as assessed by CDR-SB and ADAS-Cog 14 (**Figure 9** in Appendix 3.2). These findings are consistent with the previous findings from Study 201 as documented in the clinical pharmacology review of original BLA 761269.

2.3.2 Is the proposed dosing regimen appropriate for the general patient population and subpopulations based on intrinsic factors?

Yes. The recommended dosing regimen of lecanemab 10 mg/kg biweekly was used in the pivotal Phase 3 Study 301 and supported by the Phase 2 Study 201. Study 201 demonstrated a dose-dependent reduction in brain amyloid and dose-dependent slowing in cognitive decline on CDR-SB and ADAS-Cog14 compared to placebo. Lecanemab 10 mg/kg biweekly dosing achieved greatest brain amyloid reduction and greatest slowing in cognitive decline (refer to original BLA761269 clinical pharmacology review). In Study 301, lecanemab 10 mg/kg biweekly dosing has shown significant clinical effects at 18 months, significant reduction in brain amyloid as measured by PET, and an improvement of downstream neuropathology as measured by biomarkers such as plasma Aβ42/40 ratio and plasma p-tau181 (refer to Section 2.3.1).

The selected dose of lecanemab was also supported by exposure-dependent slowing of decline on CDR-SB and ADAS-Cog14 over time. Across the tested doses in studies 201 and 301, lecanemab 10 mg/kg biweekly dosing resulted in the highest exposures and showed greatest slowing in cognitive decline on CDR-SB and ADAS-Cog14 (**Figure 6** in Appendix 3.2). Similar exposure-response relationships were

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[1] Chatterjee et. al., Plasma glial fibrillary acidic protein is elevated in cognitively normal older adults at risk of Alzheimer's disease. Transl Psychiatry. 2021 Jan 11;11(1):27.
[2] Pereira et. al., Plasma GFAP is an early marker of amyloid-β but not tau pathology in Alzheimer's disease. Brain. 2021 Dec 16;144(11):3505-3516.
[3] Tarawneh et. al., Diagnostic and Prognostic Utility of the Synaptic Marker Neurogranin in Alzheimer Disease. JAMA Neurol. 2016 May 1;73(5):561-71.
[4] Wellington et. al., Increased CSF neurogranin concentration is specific to Alzheimer disease. Neurology. 2016 Mar 1;86(9):829-35.
[5] Kvartsberg et. al., Cerebrospinal fluid levels of the synaptic protein neurogranin correlates with cognitive decline in prodromal Alzheimer's disease. Alzheimers Dement. 2015 Oct;11(10):1180-90.

observed with Amyloid PET Centiloid, plasma Aβ42/40 ratio, and plasma p-tau181 (**Figure 7** and **Figure 8** in Appendix 3.2).

Lecanemab 10 mg/kg biweekly dosing was generally well-tolerated. In Study 301 Core, 12.6% of subjects on 10 mg/kg biweekly treatment had ARIA-E and less than 3% were symptomatic. Rates of treatment-emergent adverse events across subgroups were consistent with the overall population, except for the incidence of ARIA-E which was higher in *APOE* ε4 carriers, in particular *APOE* ε4 homozygotes. Please refer to **Section 2.3.3** and clinical review for additional details on assessments and recommendations related on *APOE* genotype.

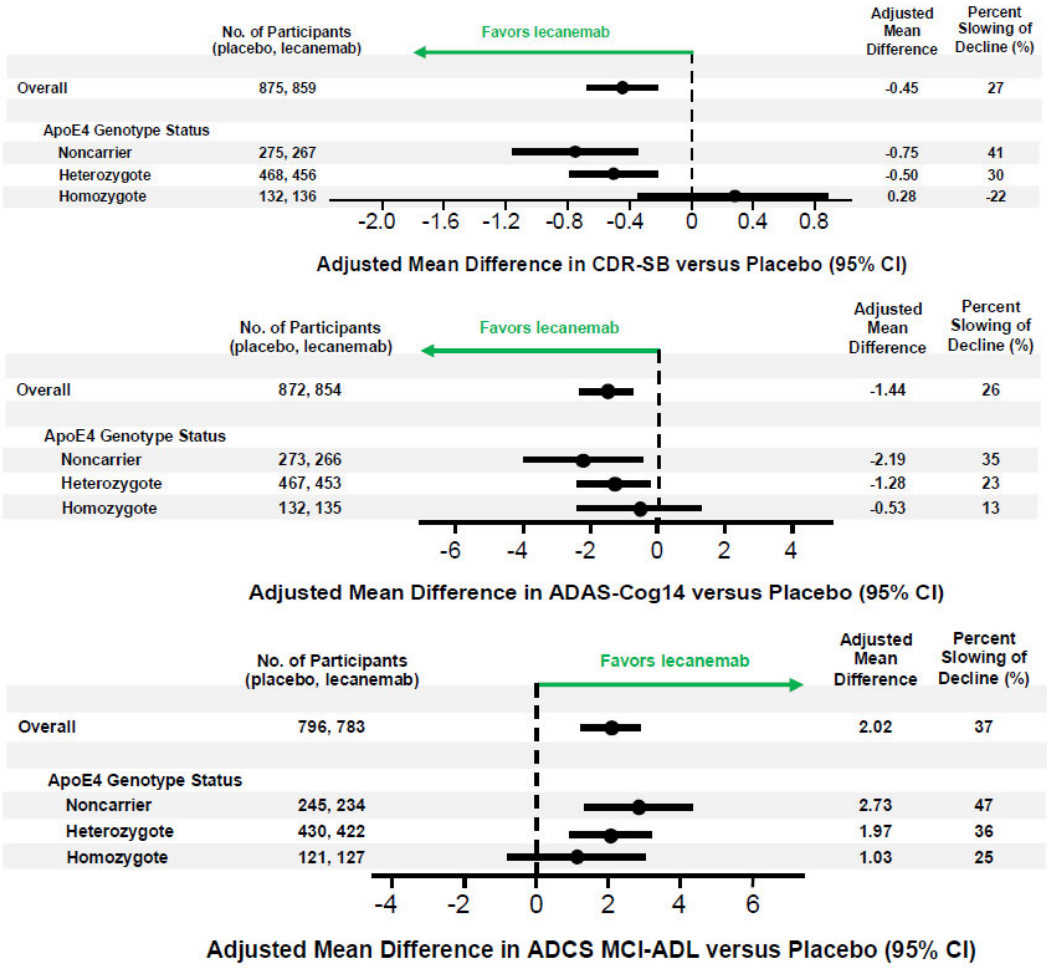
Dose adjustment is not necessary based on intrinsic factors such as age, race, sex, body weight, renal or hepatic impairment. Population pharmacokinetic analysis using pooled data from studies 101, 104, 201, and 301 suggested that sex, body weight, and albumin were found to impact exposure to lecanemab. However, none of these covariates were found to be clinically significant. Please refer to original BLA 761269 clinical pharmacology review for impact of intrinsic factors on PK of lecanemab.

2.3.3 What clinical pharmacology information is available to inform the assessment of benefit and risk in subgroups with different APOE genotypes?

In Study 301, 15% (274/1795) of patients in both treatment arms were *APOE* ε4 homozygotes, 53% (957/1795) were heterozygotes, and 31% (564/1795) were noncarriers. According to Applicant's pre-specified subgroup analysis (**Figure 3**), the change from baseline in all three clinical endpoints (CDR-SB, ADAS-Cog14, and ADCS MCI-ADL) favored lecanemab treatment compared to placebo across different *APOE* genotypes, except for CDR-SB in *APOE* ε4 homozygous patients. There appeared to be a treatment-by-genotype effect on the basis of *APOE* genotype. Specifically, a stepwise reduction in clinical benefit was observed for *APOE* ε4 noncarrier, heterozygote, and homozygote across the three clinical endpoints (**Figure 3**). To inform the benefit assessment of lecanemab treatment for patients with different *APOE* genotypes, the review team evaluated the impact of *APOE* genotype based on exposure-response analysis and plasma/CSF biomarker data as summarized below.

The observed difference in the magnitude of treatment benefit between subgroups with different *APOE* genotypes has not been fully elucidated. The review team examined the amyloid PET Centiloid levels across *APOE* genotypes in Study 301, which suggested higher baseline amyloid PET Centiloids in *APOE* ε4 carriers than noncarriers (Appendix 3.2.5.1 **Figure 10)**. It should be noted that the baseline amyloid PET and reduction of from baseline was similar between *APOE* ε4 homozygous and heterozygous subgroups in Study 301, which does not explain the difference in clinical outcome between these two subgroups (Appendix 3.2.5.1 **Figure 10**).

Figure 3 Forest Plot of Adjusted Mean Difference from Baseline for Clinical Endpoints by *APOE* Genotype at 18 Months in CDR-SB, ADAS-Cog14, and ADCS MCI-ADL in Study 301 Core



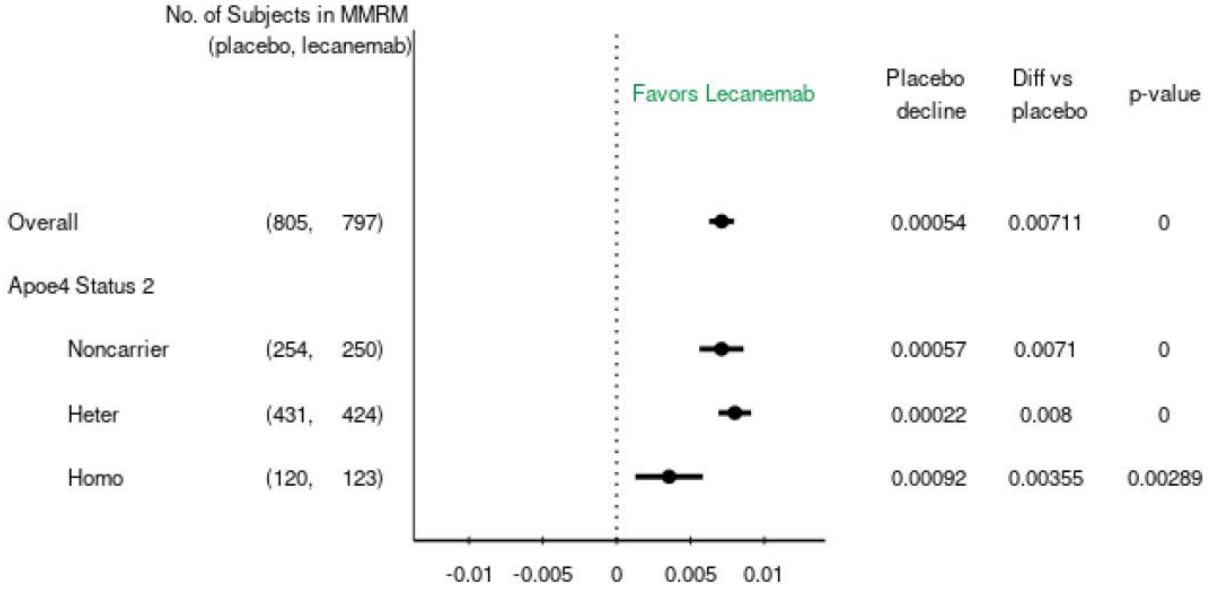
Source: Applicant's Clinical Overview, page 84, Figure 14

The Applicant explored the potential impact of *APOE* genotype on amyloid PET and efficacy endpoints using exposure-response analysis. The analysis based on pooled data from studies 201 Core and 301 Core has identified *APOE* ε4 carrier status as a statistically significant predictor of baseline amyloid PET, but not for drug effect. Adding *APOE* genotype (*APOE* ε4 heterozygous/homozygous) did not provide any statistically significant improvement to the exposure-response model for amyloid PET or CDR-SB. These results should be taken with caution, given the small number of homozygous subjects treated with lecanemab (16%, 242/1499) and the high ETA shrinkage on the drug effect Inter-individual variability estimate. Please refer to Appendix 3.2.5 for additional details for exposure-response analysis related to *APOE* genotype.

Further, a consistent pattern of favoring lecanemab treatment was observed In Study 301 Core across plasma biomarkers (Aβ42/40 ratio, p-tau181) and CSF biomarkers (Aβ[1-42], t-tau, p-tau181) for all the genotypes, including *APOE* ε4 homozygotes. Representative forest plots are shown in **Figure 4**.

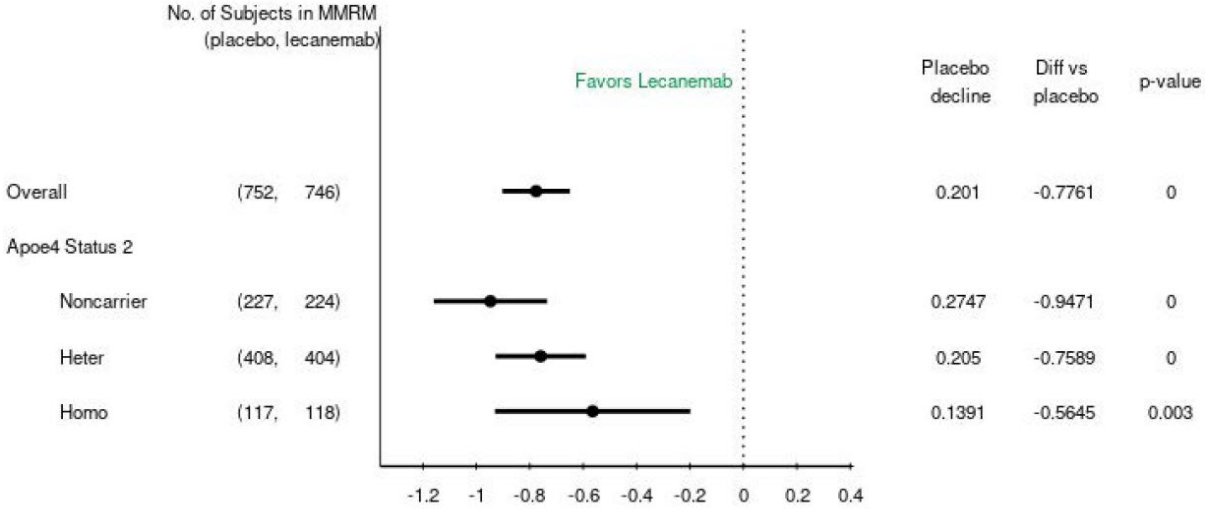
Figure 4 Forest Plots of Adjusted Mean Difference from Baseline for Biomarkers by *APOE* Genotype.
(A) plasma Aβ42/40 ratio; (B) plasma p-tau181; (C) CSF Aβ[1-42]; and (D) CSF p-tau181

A



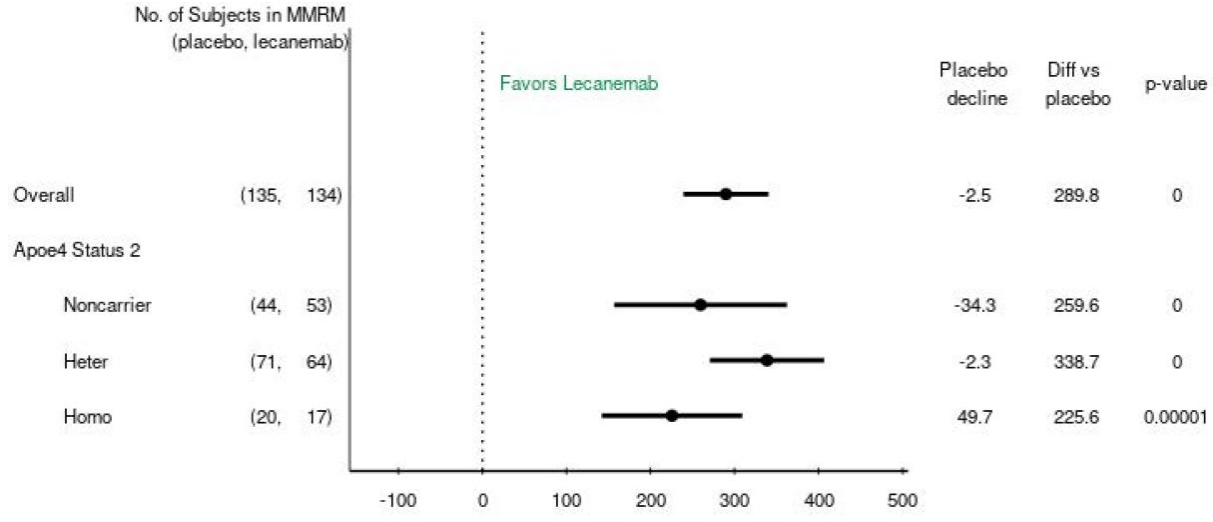
Adjusted mean difference vs placebo (95% CI for difference) in plama Abeta42/40 ratio

B



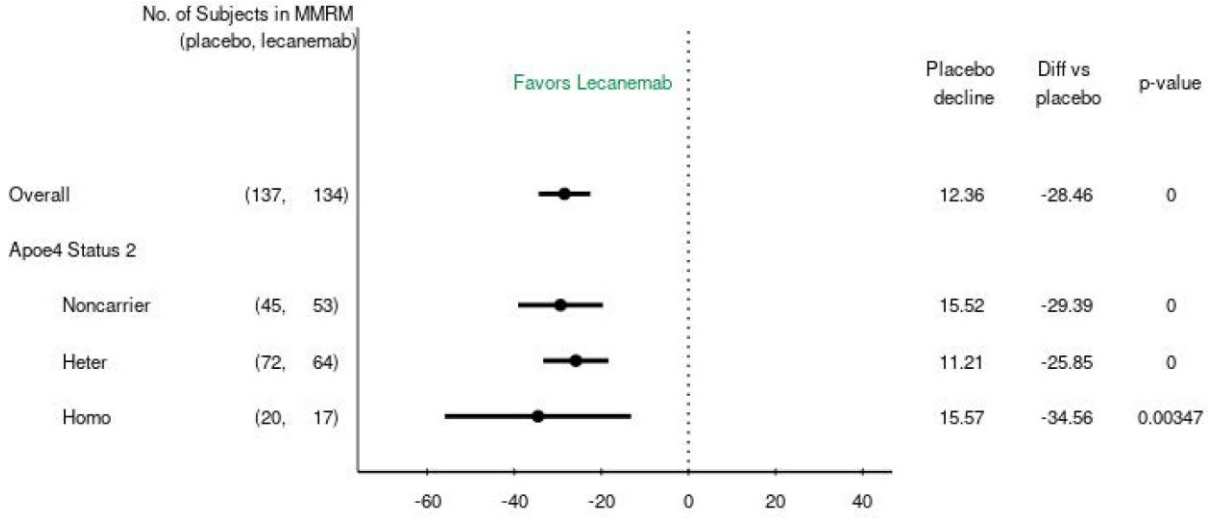
Adjusted mean difference vs placebo (95% CI for difference) in plasma ptau181

C



Adjusted mean difference vs placebo (95% CI for difference) in CSF Abeta1-42

D



Adjusted mean difference vs placebo (95% CI for difference) in CSF ptau181

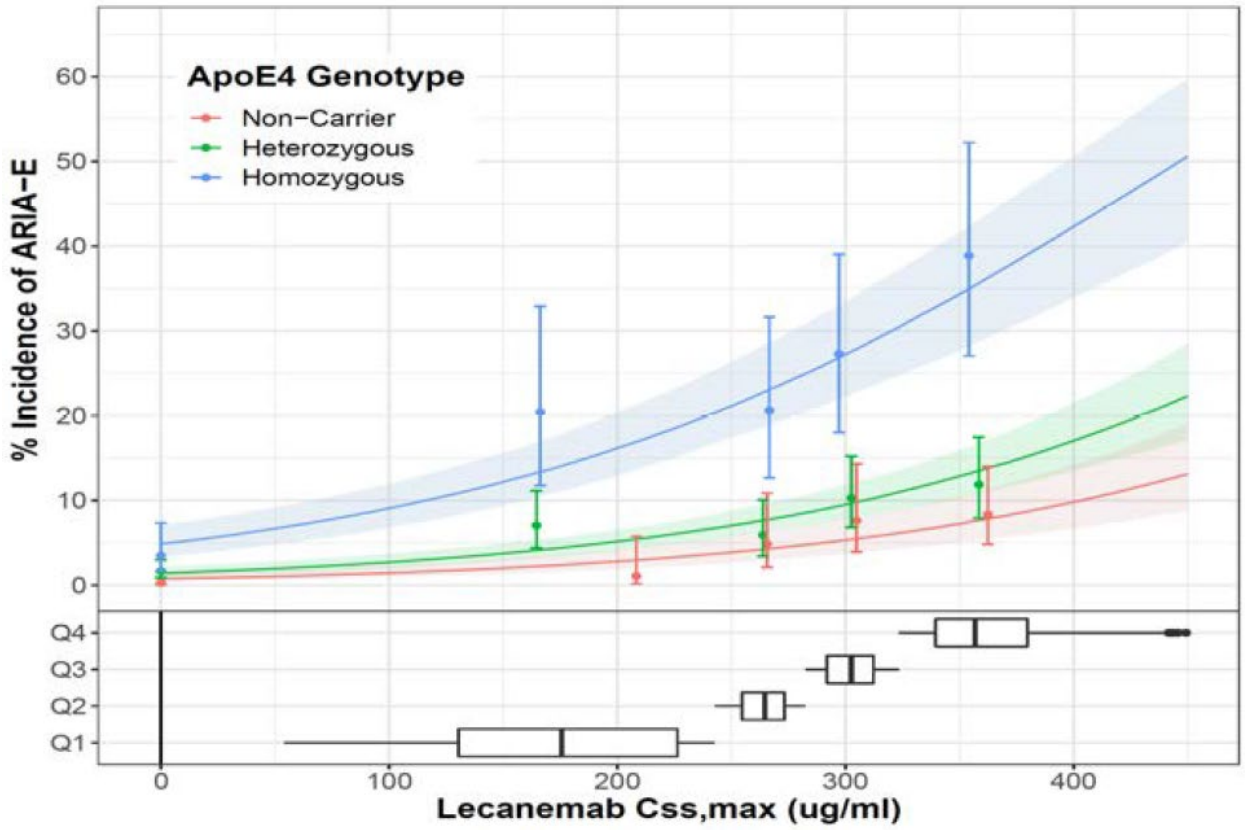
Source: Applicant's Clinical Overview, page 85-86, Figures 15 and 16, and Applicant's Information Request Response submitted on Jun 15, 2023.

Lecanemab was relatively well tolerated, however, serious adverse events were noted in both ARIA-E and ARIA-hemorrhage (ARIA-H). Applicant's exposure-response modeling identified Css,max as the best predictor of incidence of ARIA-E, with *APOE* ε4 carrier status as a significant covariate. Following lecanemab 10 mg/kg biweekly treatment (mean Css,max 305 µg/mL), the ARIA-E incidence rate was predicted to be higher (28%) in *APOE* ε4 homozygotes compared to that in *APOE* ε4 heterozygotes (9.85%) and *APOE* ε4 noncarriers (5.45%), consistent with the observed data (**Figure 5**). The ARIA-H incidences were higher in *APOE* ε4 homozygotes compared to heterozygotes and non-carriers, while no clear correlation between exposure parameters and isolated ARIA-H incidence rate was observed across

APOE genotypes. Refer to Appendix 3.2.5 for additional details regarding exposure-response analysis for safety endpoints.

Based on the observations above, the review team recommends describing the benefit/risk assessment based on *APOE* genotypes in labeling. Specifically, the increased risk of ARIA in *APOE* ε4 homozygotes need to be described. In addition, the team recommends an adequate description in labeling Section 14 regarding the subgroup findings for efficacy by *APOE* genotype, including the clinical endpoints (CDR-SB, ADAS-Cog14, ADCS MCI-ADL) and disease-relevant biomarkers (amyloid beta PET, plasma Aβ42/40 ratio, plasma p-tau181), to inform the benefit risk assessment.

Figure 5 Observed and Model-Predicted ARIA-E Incidence vs. Model-Predicted Lecanemab Css,max



Source: Applicant's Clinical Pharmacology Summary, page 71, Figure 18. In the top panel, filled circles represent pooled Study 301 Core and Study 201 Core observed incidence of ARIA-E for each lecanemab Css,max quartile and placebo, plotted at the median Css,max of each group. Whiskers represent 95% confidence interval of the observed ARIA-E incidence. Solid simulated lines represent the model-predicted % incidence of ARIA-E in *APOE* genotypes. The shaded areas represent the 95% confidence interval of the predicted incidence. In the bottom pane, the range of model-predicted Css,max values for the total Study 301 Core and Study 201 Core analysis set in each quartile is displayed.

Please refer to Appendix 3.3 Pharmacogenomics Review and the Clinical Review by Dr. Kevin Krudys for further details regarding the impact of *APOE* genotype on benefit and risk assessment of lecanemab.

3. APPENDICES

3.1 Summary of Bioanalytical Method Validation and Performance

3.1.1 Bioanalysis of lecanemab in human serum

In Study 301, concentrations of lecanemab in human serum was determined using a LC-MS/MS method (BTM-1425-R3). The method validation reports (EIS-R1696 and E1S-R1696A2) were previously reviewed for the original BLA submission. The method validation and performance were both adequate according to the standards in the FDA Bioanalytical Method Validation guidance.

In the original submission, the method was validated except that a small fraction of serum samples exceeded the established long-term stability duration, as described in the Appendix 4.1.1.2 in BLA 761269 clinical pharmacology review for original approval. In the current submission, the Applicant provided an additional addendum (eis-r1696a5r1) in the information request (IR) response submitted on May 24, 2023, which supported the stability of lecanemab in serum for up to 1279 days of storage at -70°C and adequately covers the storage duration of samples in Study 301 (1231 days, report 110-r10680).

3.1.2 Bioanalysis of plasma and CSF biomarkers

3.1.2.1 Aβ42 and Aβ40 in plasma

The applicant used a validated method (135087.2. (b) (4) to measure Aβ42 and Aβ40 in plasma samples from clinical study BAN2401-G000-301. The method was previously used to analyze study samples from study BAN2401-G000-201 in the initial BLA submission. A review of this method was included in the BLA 761269 clinical pharmacology review dated January 6, 2023. This supplement does not contain new stability information.

Insufficient long-term stability assessment conducted in method validation (135087.2. (b) (4):

(b) (4)

Overall, the submitted stability information does not support the study sample storage in study BAN2401-G000-301. As stated in the original review, the stability data does not meet the industry standard to demonstrate analyte stability.

In summary, the submitted stability information does not meet the industry standard or comply with FDA recommendation to demonstrate analyte stability, Therefore, the reliability of Aβ42 and Aβ40 concentration data in plasma samples from study BAN2401-G000-301 cannot be assured. However, even with the uncertainties in long-term stability assessment, the increase in plasma Aβ42/40 ratio observed in Study 301 Core with lecanemab compared to placebo (Section 2.3.1 **Figure 2A**) is unlikely a random occurrence. Hence, the review team recommends including a qualitative description in the labeling to reflect the trend of change, and including a disclaimer statement to highlight the uncertainties in bioanalysis where quantitative data on plasma Aβ42/40 ratio appear in the label. The labeling approach remains the same with original approval.

3.1.2.2 Aβ42 and Aβ40 in CSF

The applicant developed two methods using the Lumipulse® G -amyloid $_{1-42}$ and Lumipulse® G -amyloid $_{1-40}$ assay kits to quantify β-amyloid (1-42) and β-amyloid (1-40) in CSF specimens. (b) (4) The test kit contains lyophilized calibration standards and quality control samples (QCs) for use.

The intra-assay precision for β-amyloid (1-42) assay was evaluated by analyzing 20 replicates of 3 levels of QCs (339.4, 766.9, and 1188.2 pg/mL) within an analytical run. Inter-assay precision was evaluated using 3 levels of QCs (394.4, 753.0, and 1162 pg/mL) in multiple analytical runs, i.e., once a day, over 10 days. The assay precision was ≤1.6% and ≤2.0% for intra- and inter-assay runs, respectively.

The intra-assay precision for β-amyloid (1-40) assay was evaluated by analyzing 20 replicates of 3 levels of QCs (4036.1, 9946.5, and 19594.8 pg/mL) within an analytical run. Inter-assay precision was evaluated using 3 levels of QCs (4081.7, 10227.2, and 20005.4 pg/mL) in multiple analytical runs, i.e., once a day, over 10 days. The assay precision was ≤1.8% and ≤2.2% for intra- and inter-assay runs, respectively.

The applicant performed linearity, sensitivity, accuracy, and dilutional linearity (**Table 1**). The applicant did not perform stability studies. (b) (4) .

Insufficient long-term stability assessment:

(b) (4) . Therefore, the stability of the analyte in CSF from study BAN2401-G000-301 cannot be assured.

In summary, the submitted stability information does not meet the industry standard or comply with FDA recommendation to demonstrate analyte stability. As such, the reliability of β-amyloid (1-42) and β-amyloid (1-40) concentrations data in the CSF samples from study BAN2401-G000-301 cannot be assured. However, even with the uncertainties in long-term stability assessment, the increase in Aβ[1-42] in CSF observed in Study 301 Core with lecanemab compared to placebo (Section 2.3.1 **Figure 2B**) is

unlikely a random occurrence. Hence, the review team recommends including a qualitative description in the labeling to reflect the trend of change.

Table 1 Bioanalytical validation for determination of β -Amyloid (1-42) and β -Amyloid (1-40) in human CSF by CLEIA

Analyte	**β -Amyloid (1-42)**	**β -Amyloid (1-40)**
Validation Report	ab42-csf-lumipulse-2017	ab40-csf-lumipulse-2019
Measurement range	12.0 to 2102.0 pg/mL	6.0 to 30,525.7 pg/mL
Intra-assay precision	≤1.6%	≤1.8%
Inter-assay precision	≤2.0%	≤2.2%
Sensitivity (LLOQ)	9 pg/mL	5 pg/mL
Accuracy	within ±3SD of the expected manufacturer's targets	within ±3SD of the expected manufacturer's targets
Dilution integrity	1:10	1:2, 1:5, 1:10, 1:20
Parallelism	Not assessed	Not assessed
QC sample bench-top stability	Not assessed	Not assessed
QC sample freeze/thaw	3 freeze (-70 °C)/thaw cycles	2 freeze (-70 °C)/thaw cycles
Processed sample stability	2 months at -20 °C	2 months at -20 °C
Long-term storage stability (Applicant report based on literature information)	(b) (4) (pending verification)	(b) (4) (pending verification)
Selectivity	Not assessed	Not assessed

3.1.2.3 p-tau181 in plasma

In Study 301, phosphorylated Tau 181 (p-tau181) concentration in plasma was determined using a commercial Simoa Advantage V2 Assay Kit. The method validation report (110-r11817-r1) and addendums were previously reviewed for the original BLA submission. As described in the Appendix 4.1.3.2 in BLA 761269 clinical pharmacology review for original approval, the bioanalytical method for plasma p-tau181 was not fully validated, with multiple deficiencies such as long-term stability. As a result, the original approved labeling accepted description on the trend of reduction for plasma p-tau181, while highlighted the uncertainties in bioanalysis where the quantitative data of plasma p-tau181 was listed.

In the current submission, the Applicant provided an additional addendum (110-r11817a5) in the IR response submitted on May 31, 2023, (b) (4) Considering the increase in plasma p-tau181 observed in Study 301 Core with lecanemab treatment compared to placebo (Section 2.3.1 **Figure 2C**), the review team recommends keep using the same labeling approach as the original approval for this biomarker, i.e., to include a qualitative description in the labeling to reflect the trend of change in plasma p-tau181, and to include a disclaimer statement about the uncertainties in bioanalysis where the quantitative data of plasma p-tau181 is listed in the label.

3.1.2.4 p-tau181 in CSF

The p-tau181 in human cerebrospinal fluid (CSF) was measured by chemiluminescence enzyme immunoassay (CLEIA) using the Lumipulse® G1200 automated immunoassay instrument with the commercialized kit, Lumipulse® G p-tau181 assay kit.

The CLEIA method is a specific two-step immunoassay method, which includes the following reactions:

The method was developed and validated at (b) (4) as a Research Use Only (RUO) assay. The samples from the clinical study were tested in two (b) (4) sites, one in (b) (4) and one in (b) (4). The summary of initial validation conducted at the (b) (4) site in (b) (4) is shown in **Table 2**. The validation with reagents provided by kits demonstrated the assay (b) (4)

Table 2 Method validation summary of p-tau181 in CSF

	Slope	Intercept	Error
Linearity	(b) (4)		
Analytical Measurement Range (AMR)			
Intra Assay Precision			
Inter Assay Precision			
Sensitivity (functional LLOQ)			
Accuracy			
Minimum Required Dilution			
Manual Dilution			
Automated Dilution			
Upper Limit of Quantification (ULOQ)			
Stability			
Length of run			

Sources: from the validation report: pt181-csf-lumipulse-2019.

However, the reviewer identified the following assay deficiencies:

- Inadequate assessments on the accuracy and precision (not covering the entire assay range) (b) (4)
- No data to demonstrate no drug interference in p-tau181 measurement at p-tau181 concentration (b) (4). (b) (4)
- No data to support the process and storage stability (b) (4)

- No validation data to support the suitability of the second test site – [redacted] and
- No cross-validation data to demonstrate the comparability of assay data from two [redacted] sites in [redacted]

The demonstrated assay linearity during assay validation indicates the assay can detect the dose-dependent changes of p-tau181; however, the lack of precision assessment using endogenous samples and stability assessments in the process and storage conditions raises uncertainties about the reliability of the reported p-tau181 concentration values. Considering the deficiencies mentioned above, the method is deemed suitable for describing qualitive changes only and under the condition when the change magnitude is big enough relative to the assay variability. Based on the decrease of CSF p-tau181 observed in Study 301 Core with lecanemab compared to placebo (Section 2.3.1 **Figure 2D**), the review team recommends including a qualitative description in the labeling to reflect the trend of change.

3.1.2.5 total tau in CSF

Total Tau (t-tau) in CSF was measured based on CLEIA technology on the Lumipulse® G1200 automated immunoassay instrument with Lumipulse® G Total Tau assay kit. The assay is a specific two-step immunoassay method that includes the following two reactions:

The method was developed and validated at the [redacted] site in [redacted] as a Research Use Only (RUO) assay. The samples from the study were tested in two [redacted] sites [redacted]. **Table 3** summarizes the initial validation conducted at [redacted] site in [redacted]. The validation with reagents provided by kits demonstrated the assay has good linearity over 141.0 to 1919.0 pg/mL, good precision and accuracy over ~ 300-820 pg/mL. The applicant also demonstrated no drug interference when 21 µg/mL drug is present in samples containing 270 pg/mL and 1100pg/mL total Tau. Considering the observed CSF lecanemab concentration range in samples from Study 301 (0.0162 – 6.9 µg/mL), the tested drug concertation range in interference test is sufficient.

Table 3 Method Validation Summary of total Tau in CSF

Linearity	**Slope**	**Intercept**	**Error**
	1.025	6.9	9.86 pg/mL or 2.9%
	Linear, as within Allowable Systematic Error (ASE) of 42.3 pg/mL or 12.4%.		
Analytical Measurement Range (AMR)	141.0 to 1919.0 pg/mL		
Intra Assay Precision	≤ 6.2% CV (25% of an ATE of 84.6 pg/mL or 24.9%)		
Inter Assay Precision	≤ 8.2% CV (33% of an ATE of 84.6 pg/mL or 24.9%)		
Sensitivity (functional LLOQ)	141.0 pg/mL		
Accuracy	• The accuracy was verified using 3 levels of commercial QC tested 10 times ➔ Mean result within ±3SD of the expected manufacturer's targets		
Minimum Required Dilution	N/A		
Manual Dilution	N/A		
Automated Dilution	N/A		
Upper Limit of Quantification (ULOQ)	1919.0 pg/mL		
Stability	Stable up to 48 hours when stored at ambient temperature (18-26°C)		
	Stable up to 3 freeze-thaw cycles when stored at -70°C.		
	Stable up to 2 months when stored frozen at -20°C.		
	Stable up to 5 years (60 months) when stored frozen at -70°C.		
Length of run	QC will be run once per shift and after every calibration.		

Source: from the validation report: ttau-csf-lumipulse-2017

However, the reviewer identified the following assay deficiencies,

- Inadequate assessments on the accuracy and precision (not covering the entire assay range)
  The assay range is 141.0 to 1919.0 pg/mL, but the accuracy and precision are assessed at three concentrations (approximately 300, 520 and 820 pg/mL) using QCs provided in the kit. There is no accuracy and precision data for the concentration ranges of 141-300pg/mL and 820-1919.0 pg/mL. Additionally, the precision assessment was only performed using QC samples provided in the kit. The precision assessment should include endogenous samples to evaluate the actual assay performance in study sample analysis.
- No data to support no drug interference in total Tau at total Tau concentration lower than 270 pg/mL
  As lower t-tau concentration sample is more susceptible to the drug interference if it exists, the applicant should conduct a test demonstrating no drug interference in measuring t-tau when sample concentration is at the low end of range of 140-270pg/mL even though they have demonstrated no drug interference in t-tau measurement at concentration equal or higher than 270 pg/mL.
- No data to support the process and storage stability
  The sponsor referred to the literature and manufacture's data to justify the stability during process and in storage conditions. However, the applicant did not provide original data to verify

that the process procedure, storage condition, sample condition and matrix, and assay procedure used in the literature are the same as or representative of studies in this application.

- No data to support the suitability of 30-day calibration period.
- No validation data to support the suitability of the second test site – [redacted] and
- No cross-validation data to demonstrate the comparability of assay data from two [redacted] sites [redacted]

Overall, the demonstrated assay linearity during assay validation indicates the assay can detect the dose-dependent changes of t-tau; however, the lack of precision assessment using endogenous samples and stability assessments in the process and storage conditions raises uncertainties about the reliability of the reported t-tau concentration values. Considering the deficiencies mentioned above, the method is deemed suitable for describing qualitive changes only and under the condition when the change magnitude is big enough relative to the assay variability. Based on the decrease of CSF t-tau observed in Study 301 Core with lecanemab treatment compared to placebo (Section 2.3.1 **Figure 2E**), the review team recommends including a qualitative description in the labeling to reflect the trend of change.

3.1.2.6 GFAP in plasma

In Study 301, plasma GFAP concentration was determined using a commercial Simoa GFAP Discovery Kit provided by [redacted] (validation report 1679-r12607 and sample analysis report 110-r12753). [redacted] The bioanalytical method validation met all acceptance criteria for standard calibration model, accuracy and precision, interference, parallelism and stability ([redacted]. However, the long-term stability of GFAP in plasma was demonstrated at - [redacted] (IR responses submitted on May 8, 2023 and May 31, 2023), which was shorter than the maximum storage duration 1185 days for Study 301.

A reduction in plasma GFAP was observed with lecanemab treatment compared to placebo in Study 301. However, considering the strength of available evidence on the association between anti-amyloid treatment and plasma GFAP reduction across studies and programs, as well as the limitation in bioanalytical method validation, the review team recommended not to add plasma GFAP in labeling for the current BLA supplement.

3.1.2.7 Neurogranin in CSF

An ELISA test kit provided by [redacted] was used to determine the CSF neurogranin concentration from Studies 201 Core and Study 301 (validation report neurogranin-csf-2017, sample analysis reports sar-vumc-nflp-nrgn-ykl-40-cntn-2 and sar-vumc-nfl-nrgn-csf2022). [redacted]

[redacted] (b) (4)

The review team noted that the long-term stability of neurogranin in CSF [redacted] (b) (4) was not established and does not support the storage duration of samples from studies 201 and 301. Considering the strength of available evidence on the association between anti-amyloid treatment and CSF neurogranin reduction across studies and programs, as well as the limitation in bioanalytical method validation, the review team recommended not to add CSF neurogranin in labeling for the current BLA supplement.

3.2 Pharmacometrics Analyses

The Applicant proposed to update Labeling section 12.2 to describe the exposure-response relationships in Study 301, and the description remains similar with the findings from Study 201 in the labeling of original approval. The reviewer conducted independent analysis and confirmed that the descriptions are acceptable for Study 301. The reviewer also conducted additional analysis to evaluate the influence of *APOE* genotype on the exposure-response relationships, including Amyloid PET Centiloids, efficacy and safety endpoints. The findings are summarized below.

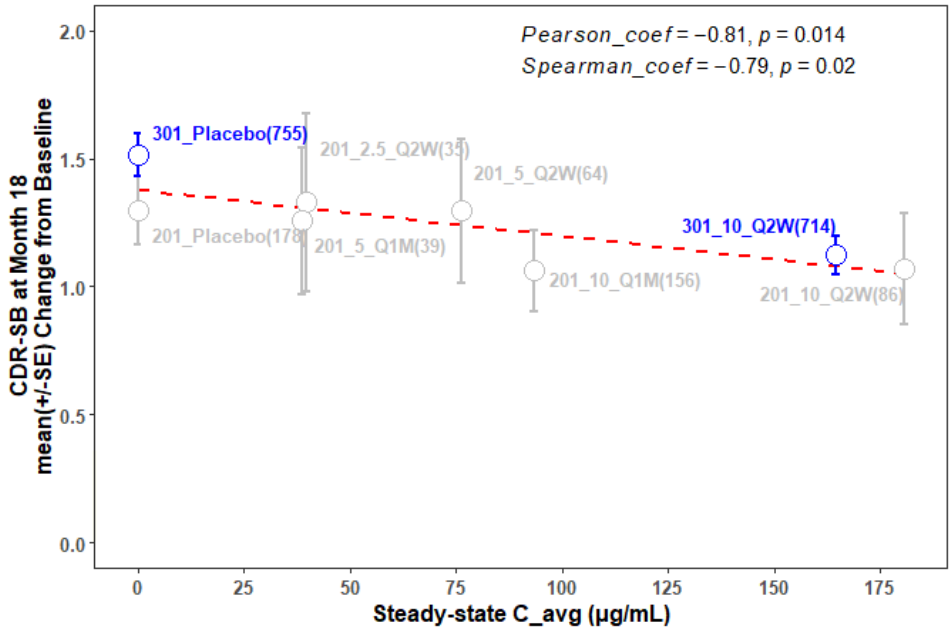
3.2.1 Exposure-Response for CDR-SB and ADAS-Cog14

Proposed Label Statement: *Model based exposure-response analyses* [redacted] (b) (4) *demonstrated that higher exposures to lecanemab-irmb were associated with greater reduction in clinical decline on CDR-SB and ADAS-Cog14.*

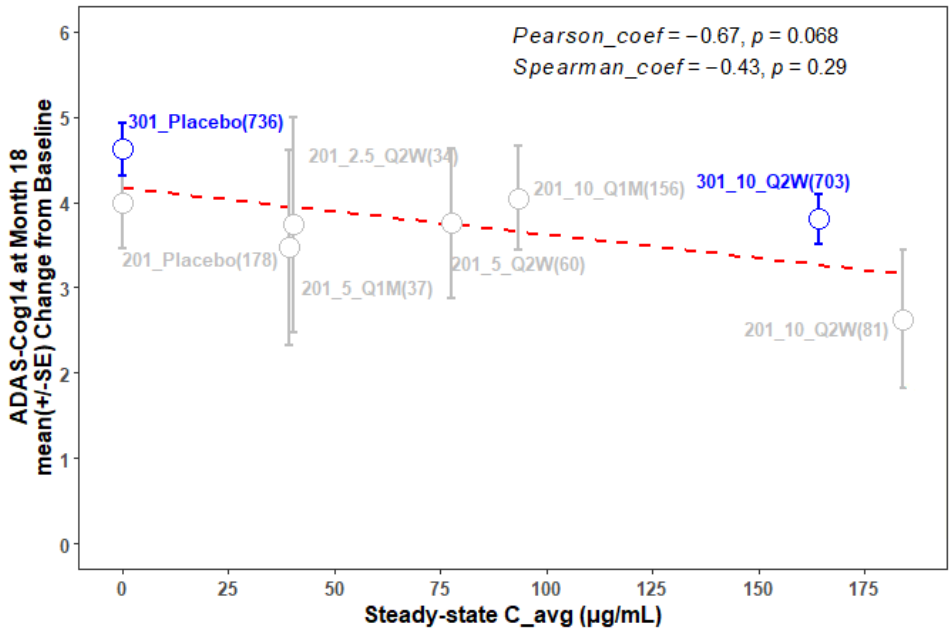
Reviewer's Comment: The analysis findings of Study 301 are consistent with Study 201 findings. As shown in the **Figure 6**, increase in PK exposures ($C_{average}$) resulted in greater reduction in clinical decline on CDR-SB and ADAS-Cog14. The applicant has also developed PK-PD models to characterize the relationship between lecanemab exposure and efficacy as measured by CDR-SB and ADAS-Cog14, which suggested exposure-dependent reduction in clinical decline on CDR-SB and ADAS-Cog14. Reviewer was able to reproduce these models and agree with overall findings.

Figure 6 Relationship of Efficacy Endpoints (CDR-SB and ADAS-Cog14) Change from Baseline at Month 18 and Average concentrations at Month 18 by Study and Treatment Arm

A. CDR-SB



B. ADAS-Cog14



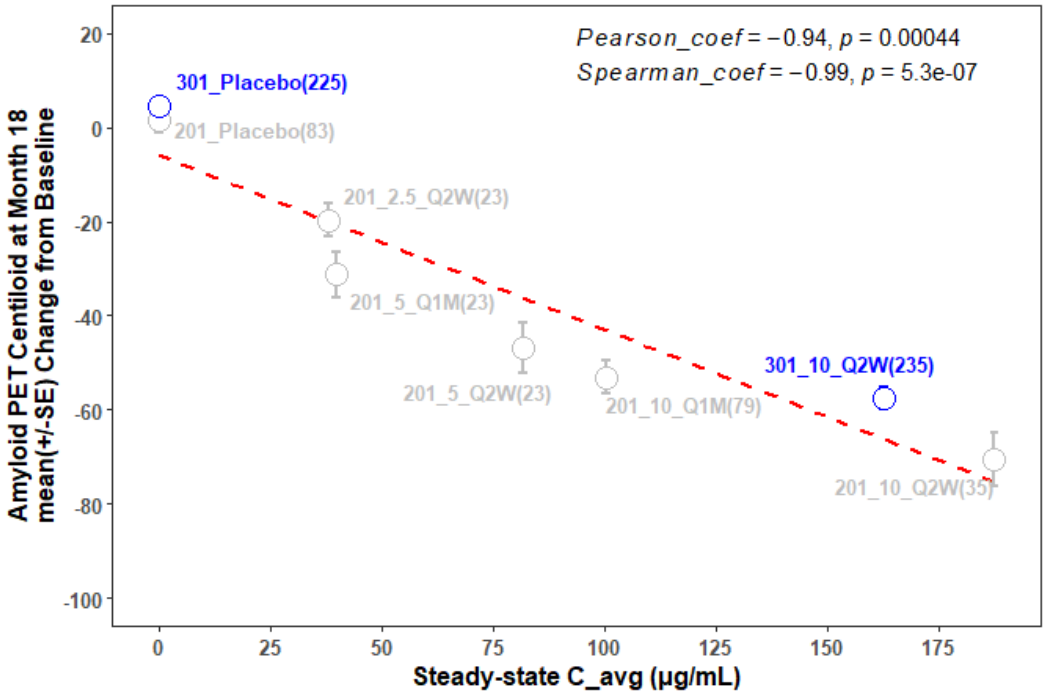
Red dashed line represents linear regressed line. Numbers in bracket represents number of subjects in the treatment group. Circles and error bars represent mean and ± standard errors respectively.
Source: Reviewer's analysis; Datasets utilized in exposure-response analysis was used for the analysis

3.2.2 Exposure-Response for Amyloid Beta Plaque

Proposed Label Statement: *In addition, higher exposures to lecanemab-irmb were associated with greater reduction in amyloid beta plaque.*

Reviewer's Comment: The analysis findings of Study 301 consistent with Study 201 findings. As shown in the **Figure 7**, higher exposures to lecanemab-irmb were associated with greater reduction in amyloid beta plaque. The applicant has also developed PK-PD models to characterize the relationship between lecanemab exposure and brain amyloid as measured by amyloid PET, which suggested concentration-dependent reduction of amyloid plaque. Reviewer was able to reproduce the PK/PD model and agree with overall findings.

Figure 7 Relationship of Amyloid PET Centiloids Change from Baseline at Month 18 and Average concentrations at Month 18 by Study and Treatment Arm



Red dashed line represents linear regressed line. Numbers in bracket represents number of subjects in the treatment group. Circles and error bars represent mean and ± standard errors respectively.
Source: Reviewer's analysis; Datasets utilized in exposure-response analysis was used for the analysis

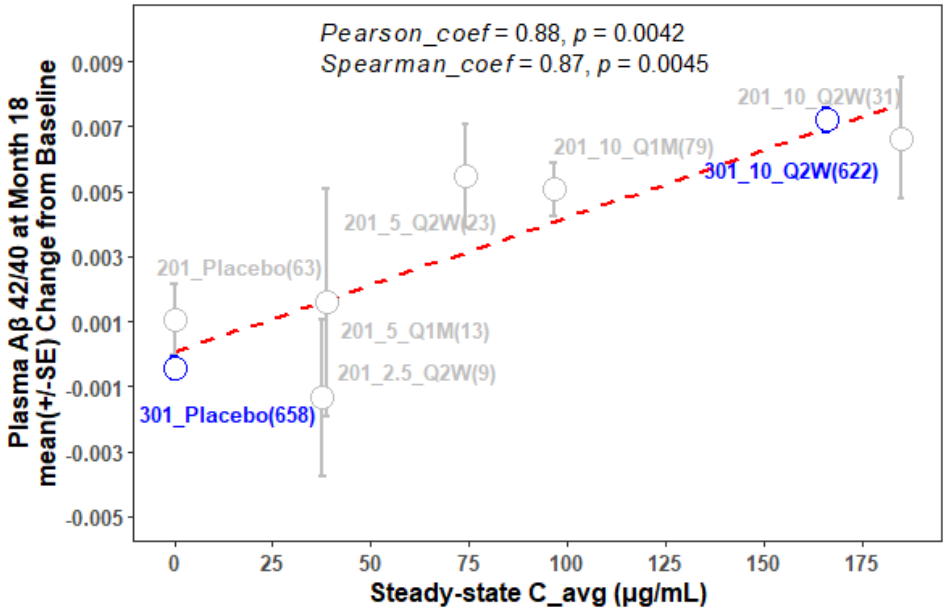
3.2.3 Exposure-Response for Plasma Aβ42/40 ratio and plasma p-tau181

Proposed Label Statement: *Higher exposures to lecanemab-irmb were also associated with greater increase in plasma Aβ42/40 ratio and greater reduction in plasma p-tau181.*

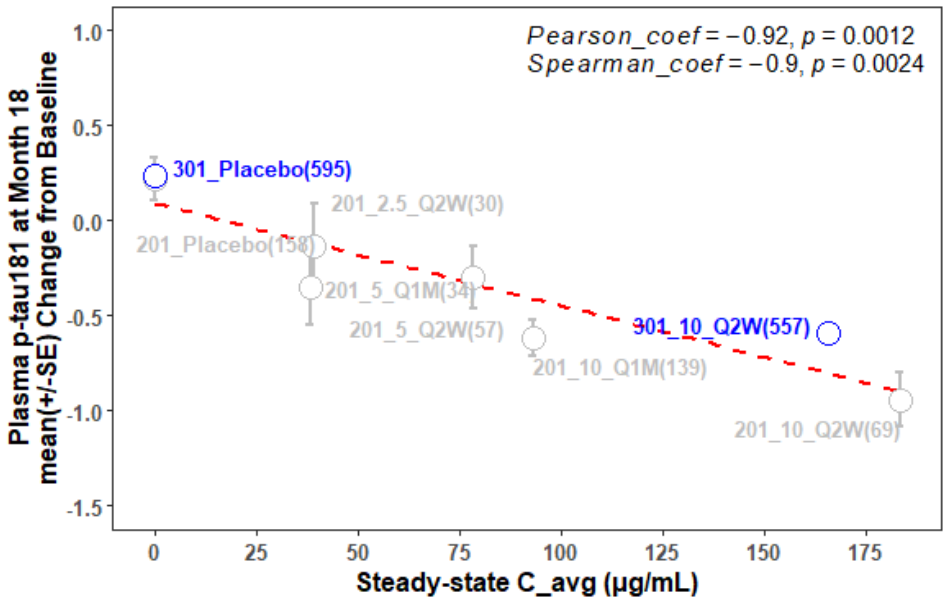
Response: The analysis findings of Study 301 are consistent with Study 201 findings. As shown in the **Figure 8**, higher exposures to lecanemab-irmb were associated with increase in plasma Aβ42/40 ratio and reduction in plasma p-tau181 at Month 18.

Figure 8 Relationship of Plasma Biomarkers (Aβ42/40 ratio and p-tau181) Change from Baseline at Month 18 and Average Concentrations at Month 18 by Study and Treatment Arm

A. Plasma Aβ42/40 ratio



B. Plasma p-tau181



Red dashed line represents linear regressed line. Numbers in bracket represents number of subjects in the treatment group. Circles and error bars represent mean and ± standard errors respectively.
Source: Reviewer's analysis; Datasets utilized in exposure-response analysis was used for the analysis

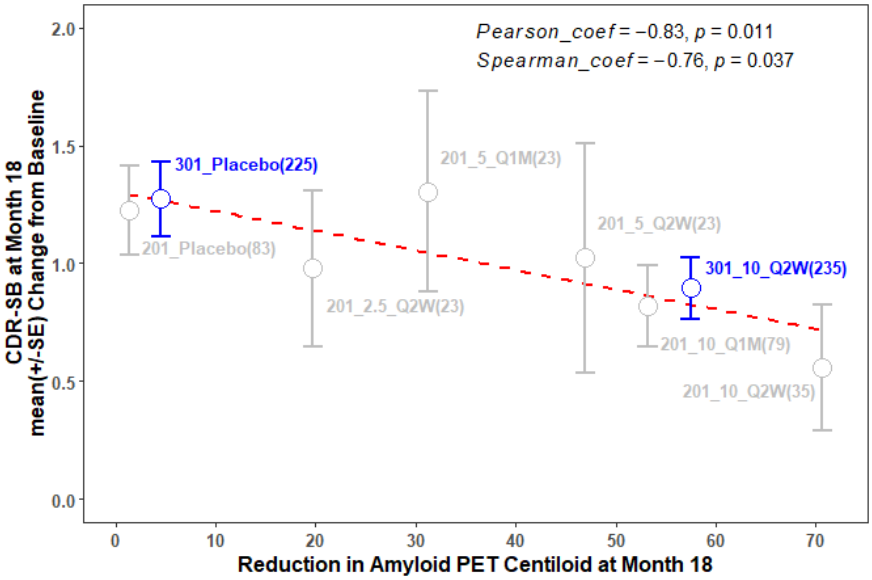
3.2.4 Association between reduction in amyloid beta plaque and clinical decline

Proposed Label Statement: *An association between reduction in amyloid beta plaque and clinical decline on CDR-SB and ADAS-Cog14 was also observed.*

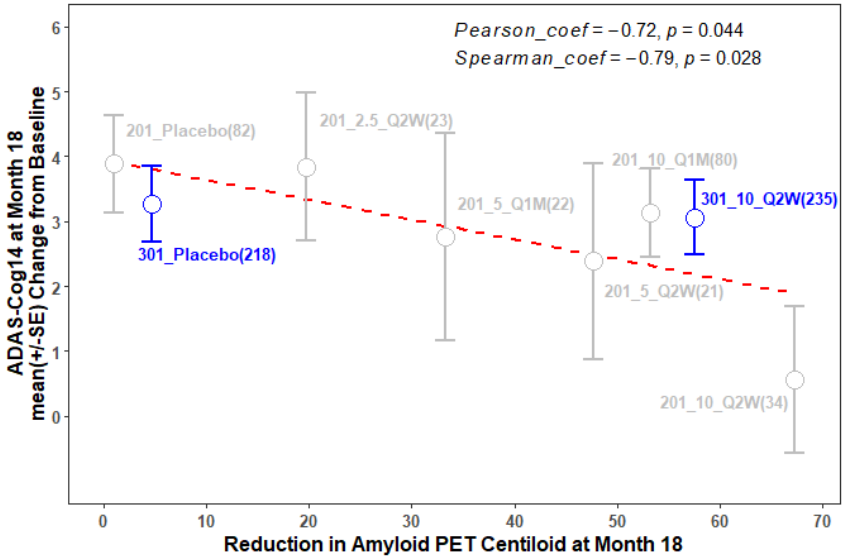
Reviewer's Comment: The analysis findings of Study 301 are consistent with Study 201 findings. As shown in the **Figure 9,** reductions in amyloid beta plaque are associated with reduction in clinical decline as assessed by CDR-SB and ADAS-Cog 14.

Figure 9 Relationship of Amyloid PET Centiloids Change from Baseline at Month 18 and Efficacy Endpoints (CDR-SB and ADAS-Cog14) Change from Baseline at Month 18 by Study and Treatment Arm

A. CDR-SB



B. ADAS-Cog14



Red dashed line represents linear regressed line. Numbers in bracket represents number of subjects in the treatment group. Circles and error bars represent mean and ± standard errors respectively.
Source: Reviewer's analysis; Datasets utilized in exposure-response analysis was used for the analysis

3.2.5 Influence of APOE Genotype on Lecanemab Exposure-Response Relationships for Amyloid PET Centiloids, efficacy and safety endpoints

The Applicant has explored the potential impact of *APOE* genotype on the final exposure-response model for biomarker-amyloid PET (Report CPMS-BAN2401-003R2-v1), efficacy-CDR-SB (Report CPMS-BAN2401-003R1-v1), and safety- ARIA-E and ARIA-H (Report CPMS-BAN2401-003R1-v1). Specially, the potential impact of *APOE* genotype was explored by adding *APOE* genotype as a potential covariate in their final exposure-response models. The key findings from these analyses are as follows:

3.2.5.1 Biomarker- Amyloid PET centiloids

The relationship between serum lecanemab concentration and the reductions in brain amyloid load (as measured by amyloid PET, in units of Centiloids) was characterized by an indirect response model with lecanemab-dependent reduction of amyloid plaque. *APOE* ε4 carrier status was identified as a statistically significant predictor of baseline amyloid PET, but not for drug effect in the final exposure-response model. Adding *APOE* genotype on baseline amyloid PET and/or drug effect did not provide any statistically significant improvement ($p<0.01$) to the model, as also suggested by the observed data (**Figure 10**).

3.2.5.2 Efficacy endpoint- CDR-SB

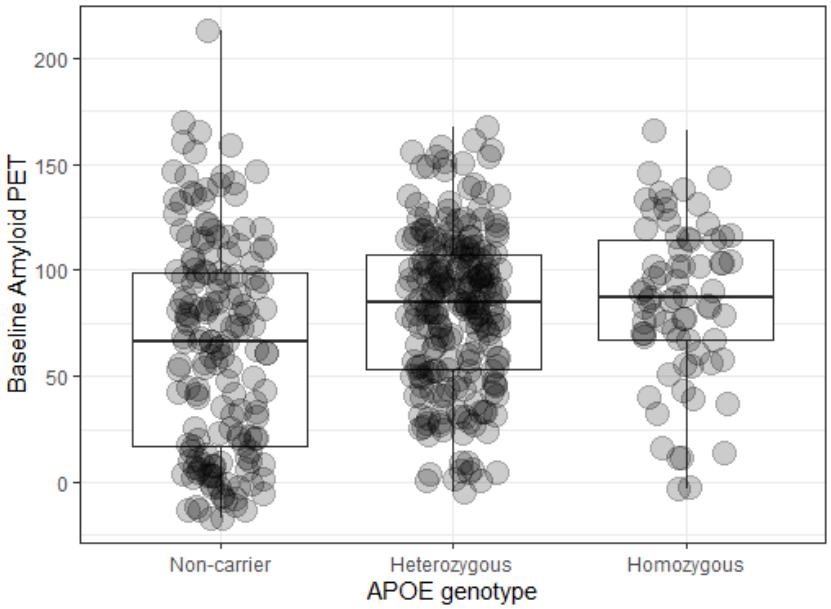
A linear disease progression model was developed to describe the disease progression of CDR-SB over time. Lecanemab effect on disease progression was introduced as exposure-dependent slowing of disease progression rate. The effect of *APOE* ε4 carrier status on drug effect was not evaluated due to high ETA shrinkage (67.6%) in the exposure-response model. Adding *APOE* genotype on drug effect did not provide any statistically significant improvement ($p<0.01$) to the model. These results should be taken with caution, given the small number of homozygous subjects treated with lecanemab (16%, n=242 out of 1499) and the high ETA shrinkage on the drug effect Inter-individual variability estimate.

3.2.5.3 Safety endpoint ARIA-E

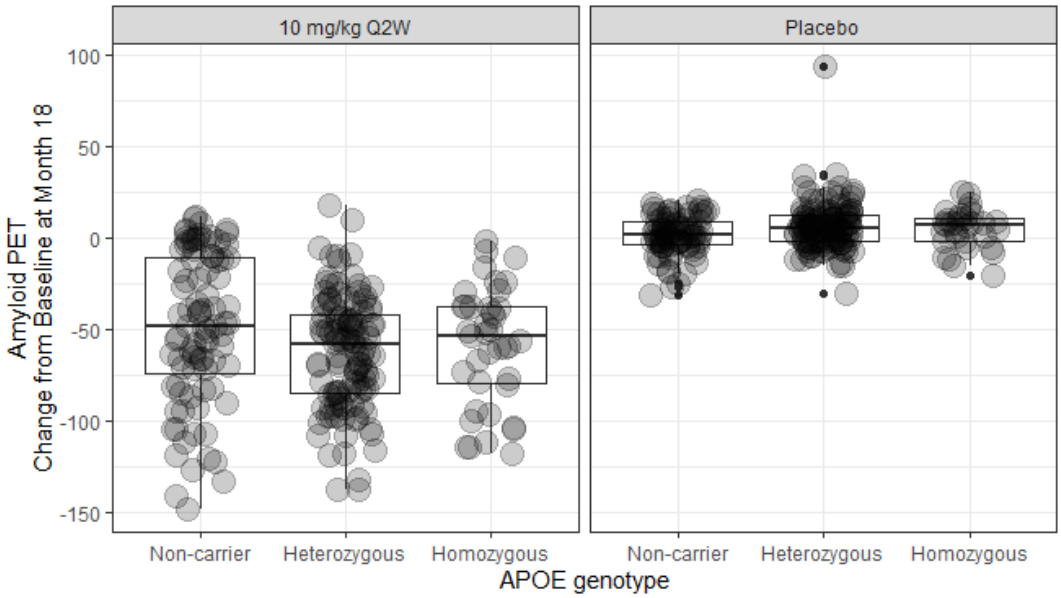
The logistic regression model describing the incidences of ARIA-E as a function of lecanemab exposure was developed with steady-state maximal concentrations as a predictor for ARIA-E incidences. *APOE* genotype status was identified as a significant predictor for ARIA-E incidences in the exposure-response model for ARIA-E incidences. ARIA-E incidence rate was predicted to be higher (28%) in *APOE* ε4 homozygotes compared to that in *APOE* ε4 heterozygotes (9.85%) and *APOE* ε4 noncarriers (5.45%), consistent with the observed data (**Figure 5**).

Figure 10 Boxplot of Baseline Amyloid PET Centiloids (A) and Amyloid PET Centiloids Change from Baseline at Month 18 (B) by *APOE* Genotype Status in Study 301

A. Baseline Amyloid PET Centiloids



B. Amyloid PET Centiloids Change from Baseline at Month 18



Source: Reviewer's Analysis

3.2.5.4 Safety endpoints- ARIA-H

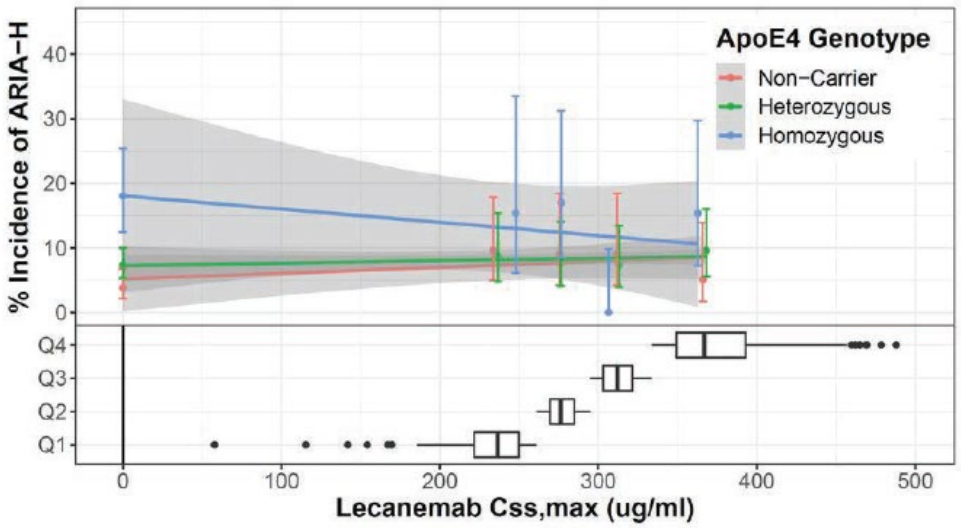
A set of graphical analyses were performed to evaluate whether the incidence of isolated ARIA-H was related to lecanemab exposure. The ARIA-H incidences were higher in *APOE* ε4 homozygotes followed by heterozygotes and non-carriers (**Table 4**). No clear correlation between exposure parameters and isolated ARIA-H incidence rate was observed across *APOE* genotypes (**Figure 11**).

Table 4 Overall Incidence (%) of Isolated ARIA-H in Study 301 by *APOE* Genotype

Treatment	Non-carrier	Heterozygous	Homozygous	Total
Placebo	3.85	7.32	18.0	7.80
Lecanemab 10 mg/kg Q2W	8.39	8.39	12.1	8.97

Source: Adapted from cpms-ban2401-003r-add-v1, Table 5

Figure 11 Isolated ARIA-H Incidence in Study 301 by *APOE* Genotype as a Function of Model-Predicted Lecanemab Css,max (μg/mL)



Source: cpms-ban2401-003r-add-v1, Figure 2

3.3 Pharmacogenomics Analyses

EXECUTIVE SUMMARY

Lecanemab is an intravenously-infused monoclonal antibody that targets soluble amyloid beta in the brain. The applicant has submitted the BLA for confirmatory approval primarily relying on a single phase 3 study (301) in 1795 patients with mild cognitive impairment due to Alzheimer's disease. The applicant genotyped all participants for *APOE* status at baseline. In a pre-specified subgroup analysis, the applicant concludes that *APOE* genotype does not appear to impact the efficacy of lecanemab. In addition, the applicant identified that there is an increased risk for both ARIA-E and ARIA-H following treatment with lecanemab based on *APOE* genotype. The purpose of this review is to evaluate the association between *APOE* genotype and the safety and efficacy of lecanemab. The findings of this review stand in contrast with those of the applicant regarding the efficacy conclusions, however we agree with the safety findings. Specifically, we conclude there is a differential treatment effect by *APOE* genotype (noncarriers, heterozygotes, and homozygotes) for the primary (CDR-SB) and secondary endpoints (ADAC-Cog-14, ADCS MCI-ADL). This is primarily supported by the consistency and directionality of the genotype-dose effect across all three clinical endpoints. In summary, our findings support that both the safety and efficacy of lecanemab vary based on *APOE* genotype and recommend that they be sufficiently described in labeling for decision making purposes.

3.3.1 Background

The Applicant (Eisai Inc.) submitted a BLA for lecanemab in the treatment of mild cognitive impairment (MCI) due to Alzheimer's Disease (AD) and mild AD, a population described as early AD. Lecanemab is a novel humanized immunoglobulin G1 (IgG1) monoclonal antibody that targets large soluble amyloid beta (Aβ) protein aggregates. According to the applicant, lecanemab distinguishes itself from other anti-amyloid mAbs in that it selectively targets large soluble protofibrils relative to monomers, with preferential activity over insoluble fibrils. The application is primarily supported by a single phase 3 study (301 core) in 1795 patients with MCI due to AD. Study 301 core serves as the confirmatory trial to verify the clinical benefit of lecanemab. Lecanemab is dosed intravenously every 2 weeks at a dose of 10 mg/kg.

Study 301 core met the primary endpoint of Clinical Dementia Rating Scale – Sum of Boxes (CDR-SB) at week 79 (p=0.00005). In addition, it met the secondary endpoints of Alzheimer's Disease Assessment Scale – Cognitive subscale with 14 tasks (ADAS-Cog 14) (p=0.00065), and Alzheimer's Disease Cooperative Study-Activities of Daily Living Scale for Mild Cognitive Impairment (ADCS MCI-ADL) (p<0.00001). In a prespecified analysis, there appeared to be a genotype dose effect for *APOE* genotype. Specifically, a stepwise reduction in improvement was observed based on *APOE* genotype with the homozygous patients not demonstrating a significant difference in CDR-SB compared to the placebo-treated subgroup.

Lecanemab was relatively well tolerated, however serious adverse events were noted in both amyloid related imagining abnormalities-edema/effusion (ARIA-E) and ARIA-hemorrhage (ARIA-H). TEAEs leading to study drug dose discontinuation were numerically higher in *APOE* ε4 carriers (LEC10-BW 7.1%) compared to *APOE* ε4 noncarriers (LEC10-BW 6.5%), largely driven by higher rates of ARIA-E in *APOE* ε4

homozygotes (LEC10-BW 46/141 [32.6%]) than *APOE* ε4 noncarriers (LEC10-BW 15/278 [5.4%]). The incidence of both ARIA-E and ARIA-H was significantly higher in *APOE* ε4 homozygous patients.

In the US, there are 2 products (lecanemab and aducanumab) approved under the accelerated approval pathway for the treatment of AD based on a reduction in amyloid beta plaques. The purpose of this review is to evaluate the association between *APOE* genotype and the safety and efficacy of lecanemab.

3.3.2 Submission Contents Related to Genomics

The distributions of *APOE* genotypes in treatment arms in Study 201 Core and 301 Core are shown in **Table 5**. Overall, 415 subjects were identified as *APOE* ε4 homozygotes, 1423 subjects were *APOE* ε4 heterozygotes, and 803 subjects were *APOE* ε4 noncarriers.

Table 5 Number of Subjects by *APOE* Genotype in Study 301 Core and Study 201 Core

Study	Treatment	*APOE4* Genotype				
		Noncarrier	Carrier	Heterozygous	Homozygous	Total
301 Core	Placebo	286	611	478	133	897
	10 mg/kg biweekly	274	618	477	141	892
201 Core	Placebo	71	174	134	40	245
	2.5 mg/kg biweekly	14	38	33	5	52
	5.0 mg/kg monthly	11	40	28	12	51
	5.0 mg/kg biweekly	8	84	70	14	92
	10 mg/kg monthly	27	224	164	60	251
	10 mg/kg biweekly	112	49	39	10	161
201 Core + 301 Core	All Treatments	803	1838	1423	415	2641

Source: page 69 Applicant's summary of clin pharm

In the pivotal study, 15.3% (274) patients were *APOE* ε4 homozygotes.

The applicant's draft labeling also provides the following in section 5: Warnings and Precautions

<u>*APOE* ε4 Carrier Status and Risk of ARIA</u>

In Study 301, 15% (274/1795) of patients in both treatment arms were apolipoprotein ε4 (*APOE* ε4) homozygotes, 53% (957/1795) were heterozygotes, and 31% (564/1795) were noncarriers. The incidence of ARIA was higher in *APOE* ε4 homozygotes than in heterozygotes and noncarriers among patients treated with lecanemab. Symptomatic ARIA-E occurred in 9.2% of *APOE* ε4 homozygotes compared with 1.7% of heterozygotes and 1.4% noncarriers. The recommendations on management of ARIA do not differ between *APOE* ε4 carriers and noncarriers [see Dosage and Administration (2.3)].

Consider testing for *APOE* ε4 status to inform the risk of developing ARIA when deciding to initiate treatment with lecanemab.

3.3.3 Key Question: Does safety and efficacy of lecanemab differ based on APOE genotype?

Yes, *APOE* genotype does appear to impact both the safety and efficacy of lecanemab. More specifically, there appears to by a genotype dose effect, with a staggered response based on the number of *APOE* ε4 alleles that the patient has for efficacy. A similar response is also observed for safety, with regard to ARIA.

3.3.3.1 APPLICANT'S ANALYSIS

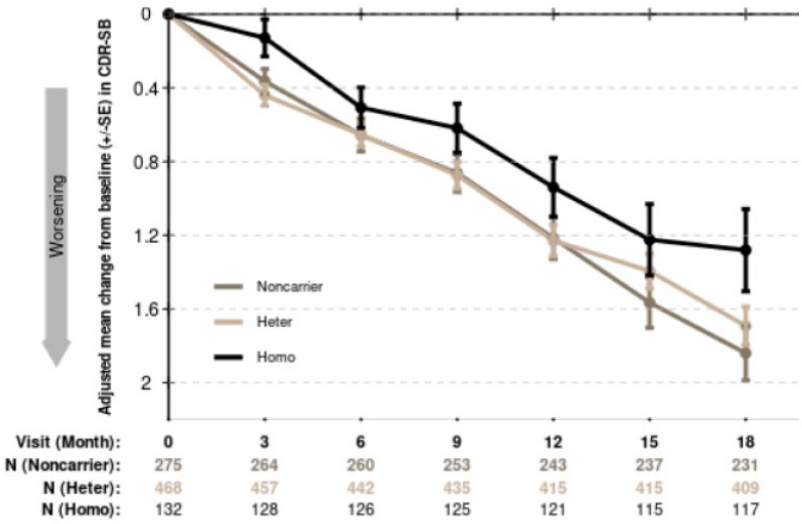
According to the Applicant, *APOE* ε4 carriers and *APOE* ε4 noncarriers both showed statistically significant differences for all clinical endpoints. Analyses by *APOE* ε4 noncarriers and *APOE* ε4 heterozygotes were statistically significant at 18 months in all 4 clinical endpoints (CDR-SB, ADAS-Cog14, ADCOMS, ADCS MCI-ADL). *APOE* ε4 noncarriers (31.4%) and *APOE* ε4 heterozygotes (53.3%) were larger populations. For the clinical endpoints of ADAS-Cog14 and ADCS MCI-ADL, results for *APOE* ε4 homozygotes favored lecanemab. For CDR-SB, PBO performed better than lecanemab in the *APOE* ε4 homozygous subgroup (**Figure 3**).

The applicant further explored the apparent incongruous finding for CDR-SB in homozygous *APOE* ε4 carriers in Study 301 Core, the following were examined in *APOE* ε4 homozygotes: performance of PBO, treatment effect, the impact of ARIA, and baseline characteristics. Of all these examinations, the performance of PBO was the most apparent explanation.

PBO performed better than lecanemab in the *APOE* ε4 homozygous subgroup on CDR-SB, which was not a randomization strata. The decline in CDR-SB in the *APOE* ε4 homozygotes receiving PBO was slower than *APOE* ε4 heterozygotes and *APOE*ε4 noncarriers (**Figure 12**), which is inconsistent with other clinical studies and observational studies (data on file from matched ADNI subjects) and may explain the less clinical benefit on CDR-SB observed in *APOE* ε4 homozygotes. Lecanemab treatment group declined faster in *APOE* ε4 homozygotes relative to *APOE* ε4 noncarriers and *APOE* ε4 heterozygotes for CDR-SB but not with the other clinical endpoints. LEC10-BW performed better than PBO on all other clinical endpoints such as ADAS-cog14 and ADCS ADL-MCI, suggesting that the CDR-SB results are inconsistent with the overall efficacy profile. Furthermore, in exposure-response modeling for CDR-SB which accounts for PBO variability, *APOE* ε4 carrier status and homozygous *APOE* ε4 status were not significant covariates, supporting consistent exposure-response across the *APOE* genotypes (refer to Appendix 3.2.5). The primary MMRM model was repeated incorporating genotype-by-treatment; this interaction term was not found to be significant.

This is not explained by adverse events such as ARIA-E (data on file). There was no difference in baseline characteristics by *APOE* genotype (data on file).

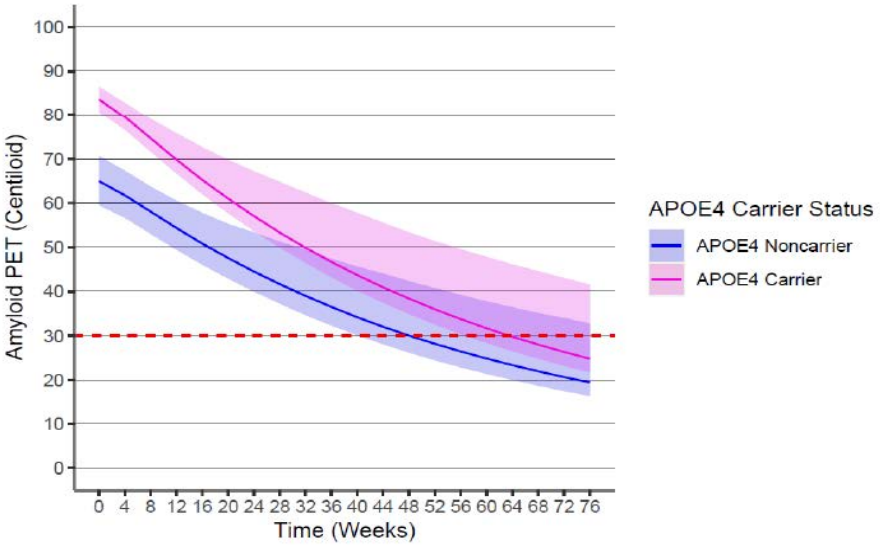
Figure 12. Placebo CDR-SB by *APOE* Genotype – Study 301 Core Intent to Treat (Full Analysis Set+)



Source: Applicant's clinical overview, page 88 Figure 18

An effect of *APOE* ε4 carrier status on baseline amyloid was found. For *APOE* ε4 noncarriers, the estimated baseline amyloid level was 65 Centiloids, while for *APOE* ε4 carriers, the value was 83 Centiloids. To demonstrate the effect of *APOE* ε4 carrier status, change in brain amyloid removal over 18 months of treatment with LEC10-BW was simulated for *APOE* ε4 carriers and *APOE* ε4 noncarriers (**Figure 13**). The higher baseline level of amyloid resulted in a faster initial rate of removal in *APOE* ε4 carriers; however at the end of the 18 month treatment period, amyloid levels were similar between *APOE* ε4 carriers and *APOE* ε4 noncarriers.

Figure 13. Model-Predicted Amyloid PET Following 18 Months of Treatment with LEC10-BW by *APOE* ε4 Carrier Status



Source: page 58 Summary of Clin Pharm. Solid line and shaded area show predicted median and 95% CI, respectively. Dashed line represents Centiloid = 30.0, indicating amyloid negative line.

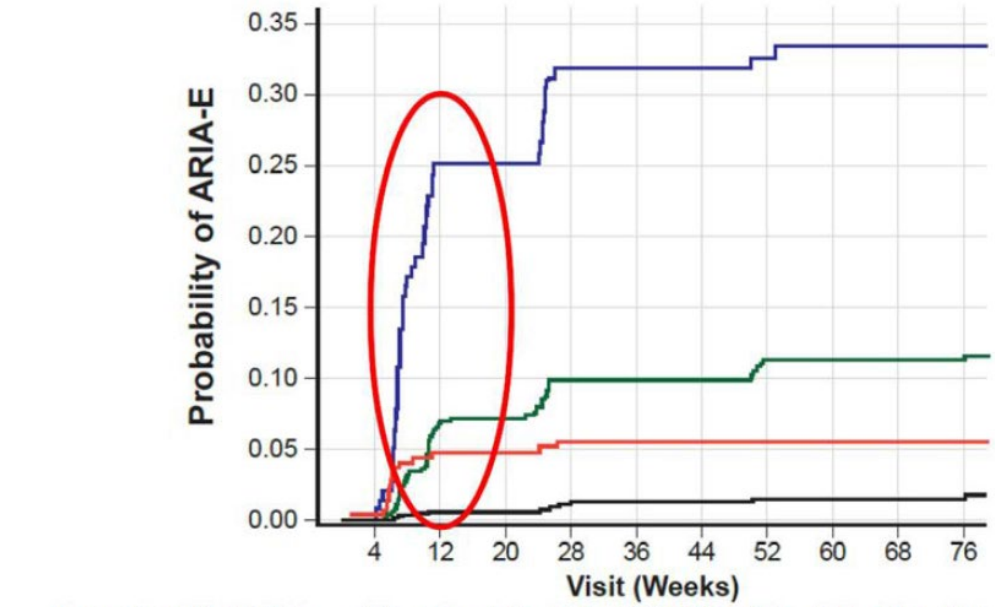
APOE Genotype and Safety

The applicant also conducted an exposure-response model for the safety endpoints. The safety endpoints of ARIA-E and ARIA-H are included here.

- **ARIA-E**

In Study 301 Core, for the first episode of ARIA-E, most cases of LEC10-BW treatment-emergent ARIA-E occurred within the first 3 months of treatment (LEC10-BW 80/113 [70.9%]) and was similar by *APOE* ε4 carrier status and *APOE* genotype (**Figure 14**).

Figure 14. Kaplan-Meier Curve of Time to First ARIA-E (Safety Analysis Set)



Source: page 96 Summary of Clin Safety

In Study 301 Core, although the incidence of ARIA-E is higher with the homozygous *APOE* ε4 carriers when treated with LEC10-BW compared to PBO, most events are mild to moderate in radiographic severity (**Table 6**).

The incidence of symptomatic ARIA-E was also low, with no subjects in PBO and 25/898 (2.8%) subjects in LEC10-BW. Although the incidence of symptomatic ARIA-E is higher with the homozygous *APOE* ε4 carriers when treated with LEC10-BW compared to PBO, most events are mild or moderate in clinical severity.

Table 6. Study 301 ARIA-E Overview

			Radiographic severity (mild/moderate/severe)		Symptomatic ARIA-E (no Symptomatic in Placebo)	Symptomatic - Clinical Severity (mild/moderate/ severe)
Status	**Placebo (N=897)**	**LEC10-BW (N=898)**	**Placebo (N=897)**	**LEC10-BW (N=898)**	**LEC10-BW (N=898)**	**LEC10-BW (N=898)**
ARIA-E	15/897 (1.7%)	113/898 (12.6%)	9 / 6 / 0	37 / 66 / 9	25 (2.8%)	10/12/3
APOE4 Carrier	14/611 (2.3%)	98/620 (15.8%)	9 / 5 / 0	31 / 57 / 9	21 (3.4%)	9/9/3
Homozygous	5/133 (3.8%)	46/141 (32.6%)	2 / 3 / 0	6 / 33 / 7	13 (9.2%)	5/7/1
Heterozygous	9/478 (1.9%)	52/479 (10.9%)	7 / 2 / 0	25 / 24 / 2	8 (1.7%)	4/2/2
APOE4 Noncarrier	1/286 (0.3%)	15/278 (5.4%)	0 / 1 / 0	6 / 9 / 0	4 (1.4%)	1/3/0

Simulated and observed incidence rate of ARIA-E by *APOE* genotype is shown in **Figure 5**. The model-predicted ARIA-E rate for *APOE* ε4 noncarriers after LEC10-BW (mean Css,max 305 µg/mL) was estimated at 5.45% (95% CI: 3.75% - 7.84%). *APOE* ε4 heterozygotes were expected to have higher rate of ARIA-E at 9.85% (95% CI: 7.96%-12.1%). The predicted rate in *APOE* ε4 homozygotes was the highest at 28.0% (95% CI: 22.6%-34.1%).

- **ARIA-H**

In Study 301 Core, the overall incidence of ARIA-H was lower in PBO (81/897 [9.0%]) than LEC10-BW (155/898 [17.3%])

Macrohemorrhage both on PBO and LEC10-BW occurred randomly throughout the course of treatment; in Study 301 Core, the subtype of macrohemorrhage occurred in 8/898 subjects overall (0.6%), or in 8/155 (5.16%) LEC10-BW subjects experiencing ARIA-H.

The overall incidence of serious TEAEs due to ARIA-H were 1 (0.1%) in PBO and 5 (0.6%) in LEC10-BW. The incidence of serious ARIA-H was lower the heterozygous *APOE* ε4 carriers (PBO 0/478; LEC10-BW 1/479 [0.20%] and *APOE* ε4 noncarriers (PBO, 1/286 [0.3%]; LEC10-BW, 2/278 [0.79%]) than in the *APOE* ε4 homozygotes (PBO, 0/133 [0%]; LEC10-BW, 2/141 [1.4%]).

The incidence rate of ARIA-H appeared to be balanced between placebo and lecanemab treatment groups. The incidence rate of ARIA-H appeared to be higher in *APOE* ε4 homozygotes compared to *APOE* ε4 heterozygotes and *APOE* ε4 noncarriers (**Table 7**).

Table 7. Incidence of Isolated ARIA-H in Study 301 Core by *APOE* Genotype

	APOE4 Genotype	Subjects Experiencing Isolated ARIA-H		
		One or More Cases	No Cases	Overall Incidence (%)
Placebo	Noncarrier	11	275	3.85
	Carrier	59	552	9.66
	Heterozygous	35	443	7.32
	Homozygous	24	109	18.0
	Total	**70**	**827**	**7.80**
LEC10-BW	Noncarrier	23	251	8.39
	Carrier	57	561	9.22
	Heterozygous	40	437	8.39
	Homozygous	17	124	12.1
	Total	**80**	**812**	**8.97**

Source: page 71 summary of clin pharm

Graphical analyses were conducted to further explore the potential relationship between isolated ARIA-H and model-predicted serum lecanemab exposure in different *APOE* genotypes. There was no apparent correlation between exposure parameters (Css,max, Css,av, and Css,min) and isolated ARIA-H incidence across *APOE* genotypes (**Figure 11**). For each *APOE* genotype, the incidence of isolated ARIA-H was balanced between PBO and lecanemab groups, with higher baseline rate for *APOE* ε4 homozygotes.

3.3.3.2 REVIEWER'S ANALYSIS

APOE Genotyping

Blood samples for *APOE* genotyping were drawn at Tier 2 of the Screening Visit. *APOE* genotyping was conducted to allow stratification of *APOE* ε4 status.

The *APOE* gene is polymorphic with three major alleles, *APOE* ε2, *APOE* ε3, *APOE* ε4, which translate into three isoforms of the protein; normal (ApoE- ε3) and Dysfunctional (ApoE- ε2 and ApoE- ε4). *APOE* genotype was determined via TaqManTM using the following SNPs *APOE* rs7412 and *APOE* rs429358 (**Table 8**).

Table 8. *APOE* Genotype to Isoform Conversion

		rs429358 (T112C)		
		TT	CT	CC
rs7412 (C158T)	TT	E2/E2		
	CT	E2/E3	E2/E4	
	CC	E3/E3	E3/E4	E4/E4

Source: apoe-sampled-2022

The applicant's methodology for *APOE* genotype was adequate for the purposes of this study.

APOE Genotype and Efficacy

Potential baseline imbalances in age, sex, BMI, and various biomarkers collected in Study 301 Core (e.g., NfL, Tau, AB 40/42, GFAP) were evaluated by *APOE* genotype group (noncarriers, heterozygotes, and homozygotes) as potential sources of variability to explain the differential response observed in both safety and efficacy following treatment with lecanemab. No significant baseline imbalances were observed in any of our analyses.

We investigated the totality of evidence surrounding *APOE* genotype and the efficacy of lecanemab. In contrast to the conclusions drawn by the applicant, it is the opinion of this review that a genotype dose effect exists for lecanemab and *APOE* genotype on the three aforementioned clinical (primary and two secondary) endpoints. This is supported by the following:

- A consistent and directional genotype effect across the three clinical endpoints CDR-SB, ADAS-Cog14, ADCS MCI-ADL is observed in **Figure 3**. Here, a clear genotype dose effect is demonstrated with the *APOE* ε4 homozygotes having a reduction in benefit. It is our opinion that this likely not due to play of chance.
- The PET substudy demonstrated a longer duration of clearance of amyloid in the *APOE* ε4 carriers (**Figure 13**). Some *APOE* ε4 carriers did not achieve amyloid clearance by week 79. Thus, it is plausible that there may be a delayed treatment effect in *APOE* ε4 homozygotes, however a difference between *APOE* ε4 carriers (heterozygous vs. homozygotes) was not demonstrated.
- *APOE* ε4 homozygosity imparts an approximate 8-12 fold increased risk for Alzheimer's and it is the most common genetic cause for Alzheimer's disease. Moreover, the risk increases in a gene-dose dependent manner (PMID: 8346443). This, coupled with differences in safety (i.e., ARIA) observed in the clinical development program, support that the differential response in *APOE* ε4 homozygotes is likely a real signal.

APOE Genotype and Safety

- No additional analyses were conducted regarding *APOE* genotype and the risk of both ARIA-E and ARIA-H.

- This increased risk is also noted in the product labeling (warnings and precautions) for the other approved product, aducanumab.
- ARIA-E was observed in 35% of patients treated with aducanumab 10 mg/kg, compared to 3% of patients on placebo. The incidence of ARIA-E was higher in apolipoprotein E ε4 (*APOE* ε4) carriers than in *APOE* ε4 non-carriers (42% and 20%, respectively).
- This review did assess other supporting evidence available in the literature. A single study was identified.
- Tolar et al., in a comprehensive review of various amyloid beta therapies (aducanumab, gantenerumab, lecanemab, and ALZ-801), did identify that the clearance of aggregated amyloid from brain vessels is associated with amyloid-related imaging abnormalities with ARIA-E and ARIA-H supported by PET imaging (PMID: 32787971). One limitation of this study is that the agents studied utilize various mechanisms of amyloid clearance.

3.3.4 Summary and Conclusions

The findings of this review generally agree with the applicant. However, our findings do stand in contrast to the applicant's conclusion that *APOE* genotype is not a significant variable that impacts the efficacy of lecanemab. The evidence for this, is supported by a consistent and directional genotype dose effect across all three clinical endpoints. In the PET sub study, there was a delayed amyloid clearance as measured by centiloids in the *APOE* ε4 carriers.

This review finds that lecanemab is approvable for the indicated population of patients with MCI due to AD. However, our findings support that both the safety and efficacy of lecanemab are different for *APOE* ε4 homozygous patients and recommend that they be sufficiently described in labeling, for decision making purposes. Moreover, we also recommend that the risk/benefit in the *APOE* ε4 homozygous population be further evaluated in the post-marketing setting.

3.3.5 Recommendations

This review recommends that the subgroup findings by *APOE* ε4 genotype and the three (CDR-SB, ADAS-Cog14, ADCS MCI-ADL) clinical endpoints be presented in section 14 in labeling for decision making purposes. This is in addition to the labeling detailing the increased risk in *APOE* ε4 homozygotes in the incidence of both ARIA-E and ARIA-H.

- **Post-marketing studies**

None.

- **Labeling recommendations**

The review team supports genotyping all patients for *APOE* status to assess the risk/benefit before initiating therapy with lecanemab.

In addition, section 14 should sufficiently describe the efficacy findings by the pre-specified *APOE* genotype group (noncarriers, heterozygotes, and homozygotes) for decision making purposes.

3.4 Immunogenicity

In Study 301 Core, the Applicant's reported incidence of treatment-emergent positive ADA and NAb following lecanemab 10 mg/kg biweekly treatment was 49/884 (5.5%) and 2/49 (4.1%), respectively, which are considerably lower than the previously reported incidence in Study 201 Core (63/154 [40.9%] and 16/63 [25.4%] for ADA and NAb, respectively) at the same dosing regimen. The Applicant stated that the differences in ADA rates between Study 201 Core and all subsequent studies may be related to refinement of the ADA assay. However, it was not clear whether the refinement made to the assay can justify the differences in the immunogenicity results.

(b) (4)

the reviewer noted that drug tolerance level for the ADA and NAb assays in Study 301 remains inadequate (b) (4) µg/mL). Please refer to OBP review for details of ADA/NAb bioanalytical method validation. This issue was previously communicated to the Applicant as PMR # 4384-2 in the action letter of original BLA 761269, which requires improvement of ADA/NAb assay methods for reanalysis of Study 301 samples.

(b) (4)

The team will re-assess the adequacy of ADA/NAb assays and the impact of immunogenicity on PK, PD, efficacy, and safety, when data to support the PMR are submitted.

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

/s/

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761269Orig1s001

OTHER REVIEW(S)

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research | Office of Surveillance and Epidemiology (OSE)
Epidemiology: ARIA Sufficiency Memorandum

Date:	July 6, 2023
Reviewer:	Danielle Abraham, PhD, MPH Division of Epidemiology I
Acting Team Leader:	Catherine Callahan, PhD, MA Division of Epidemiology I
Division Director:	CAPT Sukhminder K. Sandhu, PhD, MPH, MS Division of Epidemiology I
Subject:	ARIA Sufficiency Memorandum
Drug Name(s):	LEQEMBI (lecanemab-irmb)
Application Type/Number:	BLA-761269
Submission Number:	S001
Applicant/sponsor:	Eisai, Incorporated
OSE RCM #:	2023-5211

EXECUTIVE SUMMARY *(place "X" in appropriate boxes)*

Memo type		
-Initial		
-Interim		
-Final	X	
Source of safety concern		
-Peri-approval	X	
-Post-approval		
Is ARIA sufficient to help characterize the safety concern?	Regulatory gap: clinical safety outcomes among Alzheimer's disease patients including subpopulations	Regulatory gap: characterizing risk in broad population of Alzheimer's disease patients
-Yes		
-No	X	X
If "No", please identify the area(s) of concern.		
-Surveillance or Study Population	X	
-Exposure		
-Outcome(s) of Interest	X	X
-Covariate(s) of Interest	X	
-Surveillance Design/Analytic Tools		

A. General ARIA Sufficiency Template

1. BACKGROUND INFORMATION

1.1. Medical Product

LEQEMBI (lecanemab-irmb) is a humanized immunoglobulin G1 (IgG1) amyloid beta-directed monoclonal antibody indicated for the treatment of Alzheimer's disease.[1] Lecanemab targets aggregated forms of amyloid beta; extracellular deposits of amyloid beta are a pathophysiological feature of Alzheimer's disease.[2] Another amyloid beta-directed monoclonal antibody, aducanumab, received accelerated approval on June 7, 2021.[3] Other FDA-approved treatments for Alzheimer's disease include the cholinesterase inhibitors donepezil, rivastigmine, and galantamine along with the N-methyl-D-aspartate (NMDA) receptor antagonist, memantine.[4]

Alzheimer's disease is a neurodegenerative disease that impacts 6.7 million individuals 65 years of age and older in the United States (1). Average survival after diagnosis is four to eight years (1). Alzheimer's disease is more common in females, non-Hispanic Blacks, and Hispanics (1).

Lecanemab received accelerated approval on January 6, 2023.[5] Accelerated approval was based on the randomized, controlled trial Study 201.[6] Supplement 001 was submitted on January 6, 2023, and included the results of the confirmatory randomized, controlled trial for lecanemab (Study 301). The proposed indication for lecanemab is for the treatment of Alzheimer's disease.[7] However, the draft label states that treatment should be initiated in patients with mild cognitive impairment or mild dementia stage of disease, the population in which treatment was initiated in clinical trials.[8]

Lecanemab is administered as a 10 mg/kg intravenous infusion over approximately one hour, once every two weeks.[9] The terminal half-life of lecanemab is 5 to 7 days.[10]

1.2. Describe the Safety Concern

[1] BLA 761269 ORIG-1 Label. January 6, 2023. Silver Spring (MD), U.S. Food and Drug Administration. Accessed on June 19, 2023, at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/761269Orig1s000lbl.pdf; Krudys K. BLA 761269 (S-001) LEQEMBI (lecanemab). Clinical Efficacy Review. July 5, 2023. Silver Spring (MD). U.S. Food and Drug Administration. DARRTS Reference ID: 5202087.
[2] Mani R, Yasuda SJ, Buracchio T, Dunn B. BLA 761269 ORIG-1 Summary Review. January 6, 2023. Silver Spring (MD). U.S. Food and Drug Administration. DARRTS Reference ID: 5105619.
[3] BLA 761178 Original Approval Letter. June 7, 2021. Silver Spring (MD), U.S. Food and Drug Administration. DARRTS Reference ID: 4807032.
[4] Krudys K. BLA 761269 (S-001) LEQEMBI (lecanemab). Clinical Efficacy Review. July 5, 2023. Silver Spring (MD). U.S. Food and Drug Administration. DARRTS Reference ID: 5202087.
[5] BLA 761269 Original Approval Letter. January 6, 2023. Silver Spring (MD), U.S. Food and Drug Administration. DARRTS Reference ID: 5105416.
[6] See footnote 2
[7] Draft LEQEMBI labeling dated July 6, 2023.
[8] Ibid.
[9] Ibid.
[10] Ibid.

Overall Safety

The Division of Neurology 1 (DN1) identified several safety concerns with lecanemab. Females, Blacks, and Hispanics were underrepresented in Study 201.[11] Blacks were underrepresented in Study 301.[12] As displayed in Table 1, lecanemab exposure was associated with both amyloid-related imaging abnormalities with edema (ARIA-E), ARIA with hemosiderin deposition (ARIA-H), and intracerebral hemorrhage (>1 cm[13]), although the number of intracerebral hemorrhage cases was small.[14] ARIA is usually asymptomatic and resolves, although serious events can occur.[15] Other adverse events more common among lecanemab-exposed subjects in Study 301 Core included hypersensitivity reactions (32% lecanemab, 14% placebo), infusion related reactions (26% lecanemab, 7% placebo), and seizures (0.7% lecanemab, 0.4% placebo).[16]

Table 1. Incidence of treatment emergent ARIA and intracerebral hemorrhage in Studies 201 and 301 in placebo and those treated with lecanemab 10 mg/kg biweekly

	201 Core		201 OLE	301 Core		301 OLE
	Placebo (n=245)	Lecanemab (n=161)	Lecanemab (n=180)*	Placebo (n=897)	Lecanemab (n=898)	Lecanemab (n=1,385)†
ARIA	13 (5.3%)	20 (12.4%)	Not Provided	84 (9.4%)	191 (21.3%)	209 (15.1%)
ARIA-E	2 (0.8%)	16 (9.9%)	15 (8.3%)	15 (1.7%)	113 (12.6%)	110 (7.9%)
ARIA-H	12 (4.9%)	10 (6.2%)	28 (15.6%)	80 (8.9%)	152 (16.9%)	176 (12.7%)
Intracerebral hemorrhage >1 cm	0 (0.0%)	1 (0.6%)	1 (0.6%)	1 (0.1%)‡	6 (0.7%)‡	3 (0.2%)

*45/180=new exposures
†714/1,385=new exposures
‡Includes intracerebral hemorrhage (>1 cm) events that occurred >30 days after last dose
Source: Derived from clinical safety review (dated July 5, 2023) Table 18, Table 20, Table 64, Section 7.2.1, and Section 7.5.1; original clinical safety review (dated January 5, 2023) Table 49 and Section 7.5.2; (b) (4) (b) (4)
Abbreviations: OLE, open-label extension; ARIA, amyloid-related imaging abnormalities; ARIA-E, ARIA with edema; ARIA-H, ARIA with hemosiderin deposition (ARIA-H)

Subpopulation - ApoE ε4 Status

The proportion of subjects who were APoE ε4 carriers was greater in 301 Core than 201 Core (See Table 2). Study 301 provided longer follow-up data on patients who were APoE ε4 carriers.[17] In

[11] Erten-Lyons D. BLA 761269 LEQEMBI (lecanemab). Clinical Safety Review. January 5, 2023. Silver Spring (MD), U.S. Food and Drug Administration. DARRTS Reference ID: 5105369.
[12] Erten-Lyons D. BLA 761269 S001 LEQEMBI (lecanemab). Clinical Safety Review. July 5, 2023. Silver Spring (MD), U.S. Food and Drug Administration. DARRTS Reference ID: 5202624.
[13] Defined as >1 cm in clinical trials
[14] See footnote 12.
[15] Ibid.
[16] Ibid.
[17] Ibid.

study 201, only 49 APoE ε4 carriers were exposed to ≥1 dose of 10 mg/kg of lecanemab and only 18 with ≥6 months of exposure and 12 with ≥12 months of exposure. In Study 301, considering 301 Core and its open-label extension (OLE), 1,115 APoE ε4 carriers were exposed to ≥1 dose of 10 mg/kg of lecanemab, with 883 with ≥6 months of exposure, 691 with ≥12 months of exposure, and 517 with ≥18 months of exposure.[18]

This difference is in part due to an amendment in the protocol for 201 Core, during the study, due to safety concerns. APoE ε4 carriers (homozygotes or heterozygotes) were no longer randomized to the 10 mg/kg biweekly dose and those on 10 mg/kg biweekly treatment for ≤6 months had treatment discontinued.[19] ApoE ε4 carriers were allowed in 201 OLE.[20] Randomization in Study 301 was stratified by ApoE ε4 carrier status.[21]

Table 2. ApoE ε4 Status of subjects in Studies 201 and 301 in placebo and those treated with lecanemab 10 mg/kg biweekly

	201 Core		301 Core	
	Placebo (n=245)	Lecanemab (n=161)	Placebo (n=897)	Lecanemab (n=898)
ApoE ε4 Status				
Carrier – Heterozygote	134 (54.7%)	39 (24.2%)	478 (53.3%)	479 (53.3%)
Carrier – Homozygote	40 (16.3%)	10 (6.2%)	133 (14.8%)	141 (15.7%)
Non-Carrier	71 (29.0%)	112 (69.6%)	286 (31.9%)	278 (31.0%)

Source: Derived from clinical safety review (dated July 5, 2023) Table 5; original clinical safety review (dated January 5, 2023) Table 7
Abbreviations: ApoE, Apolipoprotein E

The incidence of ARIA was higher in APoE ε4 carriers, with the highest risk in APoE ε4 homozygotes (See Table 3). Symptomatic ARIA-E and serious adverse events of ARIA were more common in ApoE ε4 homozygotes.[22] In a published meta-analysis, there was evidence of an association between ApoE ε4 alleles and lobar intracerebral hemorrhage (2).

Table 3 Incidence of treatment emergent ARIA and intracerebral hemorrhage stratified by ApoE ε4 Status for 201 Core and 301 Core in those treated with lecanemab 10 mg/kg biweekly

	201 Core			301 Core		
	Carrier – Homozygote (n=10)	Carrier – Heterozygote (n=39)	Non-Carrier (n=112)	Carrier – Homozygote (n=141)	Carrier – Heterozygote (n=479)	Non-Carrier (n=278)
ARIA	5 (50.0%)	4 (10.3%)	11 (9.8%)	63 (44.7%)	91 (19.0%)	37 (13.3%)

[18] Erten-Lyons D. BLA 761269 S001 LEQEMBI (lecanemab). Clinical Safety Review. July 5, 2023. Silver Spring (MD), U.S. Food and Drug Administration. DARRTS Reference ID: 5202624.
[19] Erten-Lyons D. BLA 761269 LEQEMBI (lecanemab). Clinical Safety Review. January 5, 2023. Silver Spring (MD), U.S. Food and Drug Administration. DARRTS Reference ID: 5105369.
[20] Ibid.
[21] Krudys K. BLA 761269 (S-001) LEQEMBI (lecanemab). Clinical Efficacy Review. July 5, 2023. Silver Spring (MD). U.S. Food and Drug Administration. DARRTS Reference ID: 5202087.
[22] See footnote 19.

ARIA-E	5 (50.0%)	2 (5.1%)	9 (8.0%)	46 (32.6%)	52 (10.9%)	15 (5.4%)
ARIA-H*	3 (30.0%)	3 (7.7%)	3 (2.7%)	54 (38.3%)	66 (13.8%)	32 (11.5%)
Intracerebral Hemorrhage >1 cm	0 (0.0%)	0 (0.0%)	1 (0.9%)	2 (1.4%)	3 (0.6%)	1 (0.4%)

*For 201 Core presenting treatment emergent ARIA-H microhemorrhage. There was one treatment emergent superficial siderosis in a noncarrier treated with lecanemab 10 mg/kg biweekly.
Source: Derived from clinical safety review (dated July 5, 2023) Table 21; original clinical safety review (dated January 5, 2023) Table 52
Abbreviations: ApoE, Apolipoprotein E; ARIA, amyloid-related imaging abnormalities; ARIA-E, ARIA with edema; ARIA-H, ARIA with hemosiderin deposition (ARIA-H)

Subpopulation – Concomitant Antithrombotic Medications

Antithrombotics include aspirin, other antiplatelets, or anticoagulants. Subjects were not allowed to be on anticoagulants in Study 201 (unless it was for short-term use).[23] In Study 301, anticoagulants were allowed if subjects had optimized and stable anticoagulant status.[24] In both studies, subjects treated with thrombolytic drugs only had lecanemab treatment suspended until stabilization or resolution of the treated medical condition.[25] In 301 Core, aspirin was the most common antithrombotic (490/646 [75.9%] subjects taking antithrombotics).[26]

Table 4 displays the risk for ARIA-H and intracerebral hemorrhage by antithrombotic exposure. Among subjects exposed to lecanemab, there was no increased risk of ARIA-H among those with antithrombotic exposure (17%), compared to those with no antithrombotic exposure (17%) in 301 Core. There was an increased risk of intracerebral hemorrhage (0.9%), compared to those without antithrombotic exposure (0.6%), in subjects exposed to lecanemab in 301 Core. In 301 Core, among those on antithrombotics and exposed to lecanemab, the risk was most notable for those on anticoagulants (2.5%).

Table 4. Incidence of ARIA and intracerebral hemorrhage in subjects by antithrombotic exposure in Study 301 Core

	ARIA-H			Intracerebral hemorrhage		
	301 Core		301 Core + OLE	301 Core		301 Core +OLE
	Lecanemab	Placebo	Lecanemab	Lecanemab	Placebo	Lecanemab
Not on antithrombotic	93/545 (17.1%)	49/584 (8.4%)	183/991 (18.5%)	3/545 (0.6%)	0/584 (0.0%)	4/991 (0.4%)
On antithrombotic	55/328 (16.8%)	29/304 (9.5%)	105/573 (18.3%)	3/328 (0.9%)	0/304 (0.0%)	5/573 (0.9%)
Aspirin ≤ 81 mg alone	29/162 (17.9%)	13/144 (9.0%)	55/268 (20.5%)	0/162 (0.0%)	0/144 (0.0%)	0/268 (0.0%)
Aspirin > 81 mg, other antiplatelet or	15/116 (12.9%)	9/107 (8.4%)	30/206 (14.6%)	1/116 (0.9%)	0/107 (0.0%)	1/206 (0.5%)

[23] Erten-Lyons D. BLA 761269 LEQEMBI (lecanemab). Clinical Safety Review. January 5, 2023. Silver Spring (MD), U.S. Food and Drug Administration. DARRTS Reference ID: 5105369.
[24] Erten-Lyons D. BLA 761269 S001 LEQEMBI (lecanemab). Clinical Safety Review. July 5, 2023. Silver Spring (MD), U.S. Food and Drug Administration. DARRTS Reference ID: 5202624.
[25] Ibid.
[26] Ibid.

combination of aspirin and another antiplatelet						
Anticoagulation (alone or combined with other antithrombotic)	11/79 (13.9%)	7/72 (9.7%)	21/147 (14.3%)	2/79 (2.5%)	0/72 (0.0%)	4/147 (2.7%)

Source: Derived from clinical safety review (dated July 5, 2023) Table 29 & Table 78
Abbreviations: OLE, open-label extension, ARIA, amyloid-related imaging abnormalities; ARIA-H, ARIA with hemosiderin deposition

Among the 13 subjects[27] with intracerebral hemorrhage on lecanemab in the clinical development program, 8 had exposure to antithrombotics including aspirin, ticagrelor, warfarin, rivaroxaban, apixaban, and tissue plasminogen activator.[28] There were 2 deaths among subjects with intracerebral hemorrhage in those exposed to lecanemab (both in the 301 open label extension). One death was in a subject who was an ApoE non-carrier with apixaban and aspirin exposure and one in a subject who was an ApoE ε4 homozygote with tissue plasminogen activator exposure.[29]

Subpopulation – Cerebral Amyloid Angiopathy (CAA)

The definitive diagnosis of CAA is made post-mortem; however there are biomarkers of CAA such as lobar cerebral microbleeds, lobar intracerebral hemorrhage, and cortical superficial siderosis (3). Subjects with radiographic findings suggestive of CAA were excluded from Studies 201 and 301 (i.e., >4 microhemorrhages, a single intracerebral hemorrhage > 10 mm, an area of superficial siderosis).[30] There were two deaths in 301 OLE with evidence of underlying CAA. Per the clinical reviewer, "[T]he presence of an ApoE ε4 allele is associated with CAA which has an increased risk for intracerebral hemorrhage."[31]

Labeling

The July 6, 2023, draft labeling for lecanemab includes language relevant to safety concerns and risks overall and in subpopulations.[32]

There is a boxed warning for amyloid related imaging abnormalities:[33]

> *WARNING: AMYLOID RELATED IMAGING ABNORMALITIES*
>
> *Monoclonal antibodies directed against aggregated forms of beta amyloid, including LEQEMBI, can cause amyloid related imaging abnormalities (ARIA), characterized as*

[27] Six 301 Core, four 301 OLE, two 201 Core+OLE, one 101
[28] Erten-Lyons D. BLA 761269 S001 LEQEMBI (lecanemab). Clinical Safety Review. July 5, 2023. Silver Spring (MD), U.S. Food and Drug Administration. DARRTS Reference ID: 5202624.
[29] Ibid.
[30] Erten-Lyons D. BLA 761269 S001 LEQEMBI (lecanemab). Clinical Safety Review. July 5, 2023. Silver Spring (MD), U.S. Food and Drug Administration. DARRTS Reference ID: 5202624.; Erten-Lyons D. BLA 761269 LEQEMBI (lecanemab). Clinical Safety Review. January 5, 2023. Silver Spring (MD), U.S. Food and Drug Administration. DARRTS Reference ID: 5105369.
[31] See footnote 28.
[32] Draft LEQEMBI labeling dated July 6, 2023.
[33] Ibid.

ARIA with edema (ARIA-E) and ARIA with hemosiderin deposition (ARIA-H). Incidence and timing of ARIA vary among treatments. ARIA usually occurs early in treatment and is usually asymptomatic, although serious and life-threatening events rarely can occur. Serious intracerebral hemorrhages, some of which have been fatal, have been observed in patients treated with this class of medications [see Warnings and Precautions (5.1), Adverse Reactions (6.1)].

ApoE ε4 Homozygotes

Patients who are apolipoprotein E ε4 (ApoE ε4) homozygotes (approximately 15% of Alzheimer's disease patients) treated with this class of medications, including LEQEMBI, have a higher incidence of ARIA, including symptomatic, serious, and severe radiographic ARIA, compared to heterozygotes and noncarriers. Testing for ApoE ε4 status should be performed prior to initiation of treatment to inform the risk of developing ARIA. Prior to testing, prescribers should discuss with patients the risk of ARIA across genotypes and the implications of genetic testing results. Prescribers should inform patients that if genotype testing is not performed they can still be treated with LEQEMBI; however, it cannot be determined if they are ApoE ε4 homozygotes and at higher risk for ARIA [see Warnings and Precautions (5.1)].

Consider the benefit of LEQEMBI for the treatment of Alzheimer's disease and potential risk of serious adverse events associated with ARIA when deciding to initiate treatment with LEQEMBI [see Warnings and Precautions (5.1) and Clinical Studies (14)].

The relevant section of the Warnings & Precautions is provided in Appendix A. Of note, the label also provides information about a patient registry—Alzheimer's Network for Treatment and Diagnostics (ALZ-NET) registry. The label directs providers to information about the registry and advises providers to encourage patients to participate in the ALZ-NET registry. [34]

In addition to labeling, there is also enhanced pharmacovigilance in place for lecanemab, specifically for death, ARIA-E/ARIA-H, intracerebral hemorrhage >1 cm, vasculitis, and infusion reactions.[35] For ARIA-E, ARIA-H, and intracerebral hemorrhage >1 cm, cases should be reported with ApoE ε4 genotype (if available), baseline magnetic resonance imaging (MRI) findings, and concomitant medications.[36]

1.3. FDAAA Purpose (per Section 505(o)(3)(B))

Table 5. FDAAA Purpose

Assess a known serious risk	X[a]
Assess signals of serious risk	
Identify unexpected serious risk when available data indicate potential for serious risk	

[a]In alignment with the PMR/PMC development template, the FDAAA Purpose is to assess a known serious risk of ARIA and intracerebral hemorrhage (>1 cm), which will be included in the boxed warning of the updated labeling. In

[34] Draft LEQEMBI labeling dated July 6, 2023.

[35] BLA 761269 Original Approval Letter. January 6, 2023. Silver Spring (MD), U.S. Food and Drug Administration. DARRTS Reference ID: 5105416.

[36] Ibid.

addition, there are subpopulations that may have differential risks of ARIA and intracerebral hemorrhage (>1 cm). Please see section 1.4 for a complete list of additional subpopulation and outcomes of concern, along with the regulatory goal for each.

1.4. Statement of Purpose

DN1 requested that the Division of Epidemiology I (DEPI-I) conduct an assessment to determine whether the Active Risk Identification and Analysis system in the Sentinel Distributed Database (SDD) would be sufficient to assess the safety of lecanemab in a broad, overall population of Alzheimer's disease patients and three subpopulations of interest—ApoE ε4 homozygotes, patients with concomitant exposure to antithrombotics, and patients with underlying CAA. Safety concerns in these subpopulations were discussed during the June 9, 2023, Peripheral and Central Nervous System (PCNS) Drugs Advisory Committee Meeting.[37] Based on discussions with DN1, the main regulatory gaps are with respect to ARIA (including both ARIA-E and ARIA-H) and intracerebral hemorrhage (>1 cm) safety outcomes. These two safety concerns will be the primary outcomes of interest and the focus of the Active Risk Identification and Analysis system assessment[38], although, as noted in Section 1.2, there are other safety outcomes of interest.

Per DN1[39], among those exposed to lecanemab, overall, ARIA and intracerebral hemorrhage (>1 cm) are known serious risks included in the boxed warning. In addition to these known serious risks, there are subpopulations that may have differential risks of ARIA and intracerebral hemorrhage (>1 cm). Subpopulations of interest and types of risk include:

- Among ApoE ε4 homozygotes,
  - ARIA in this subpopulation is a known serious risk included in the boxed warning of the updated labeling.
  - Intracerebral hemorrhage (>1 cm) has signals of a serious risk in this subpopulation.
- Among those concomitantly exposed to an antithrombotic,
  - ARIA and intracerebral hemorrhage (>1 cm) have signals of a serious risk in this subpopulation.
- Among those with underlying CAA,
  - There is an unexpected serious risk of ARIA and intracerebral hemorrhage (>1 cm) in this subpopulation; the available data indicate potential for serious risk.

The regulatory goal differs by population and outcome.[40] The regulatory goals by population are:

- Overall population: signal evaluation for ARIA and intracerebral hemorrhage (>1 cm). This goal is consistent with the boxed warning for lecanemab for both ARIA and serious intracerebral hemorrhage. Further characterization of risk is needed in the broad, overall Alzheimer's disease population, beyond what was evaluated in the clinical trials.
- ApoE ε4 homozygotes subpopulation: signal refinement for intracerebral hemorrhage (>1 cm) and signal evaluation for ARIA.

[37] June 9, 2023: Meeting of the Peripheral and Central Nervous System Drugs Advisory Committee - FDA Briefing Document. sBLA# 761269/s-001. Lecanemab-irmb. June 9, 2023. Accessed June 23, 2023, at: https://www.fda.gov/media/169263/download.

[38] Agreed upon at the Signal Assessment Meeting (SAM) held June 23, 2023.

[39] Type of risk agreed upon at the Signal Assessment Meeting (SAM) held June 23, 2023.

[40] Regulatory goals agreed upon at the Signal Assessment Meeting (SAM) held June 23, 2023.

- Concomitant exposure to antithrombotics subpopulation: signal refinement for ARIA and intracerebral hemorrhage (>1 cm).
- CAA subpopulation: signal detection for ARIA and intracerebral hemorrhage (>1 cm).

Obtaining more precise risk estimates for ARIA and intracerebral hemorrhage (>1 cm) in a broad, overall population of Alzheimer's disease patients and among subpopulations for which data is limited could further inform labeling for ARIA and intracerebral hemorrhage (> 1 cm) risk in the postmarketing setting.

1.5. Effect Size of Interest or Estimated Sample Size Desired

The effect size of interest and the estimated sample size desired will be negotiated and determined once the draft protocol is submitted.

2. SURVEILLANCE OR DESIRED STUDY POPULATION

2.1 Population

The population of interest is patients with Alzheimer's disease. Within that population, there are several subpopulations for which further characterization of risk is needed. Those subpopulations include ApoE ε4 homozygotes, patients with concomitant exposure to antithrombotics, and patients with underlying CAA. Within those exposed to antithrombotics, there is additional interest in those on anticoagulants. Comparators for ApoE ε4 homozygotes could possibly include ApoE ε4 heterozygotes and non-carriers. Comparators for patients with concomitant exposure to antithrombotics could possibly include patients without concomitant exposure to antithrombotics. Similarly, for those on anticoagulants, a comparator could possibly be those not on anticoagulants. Comparators for patients with CAA would possibly be patients without CAA.

2.2 Is Active Risk Identification and Analysis sufficient to assess the intended population?

The Active Risk Identification and Analysis system is sufficient to identify the broad, overall population of patients with Alzheimer's disease; however, it is insufficient to identify the three subpopulations. Validated, algorithms of International Classification of Diseases, Ninth Revision, (ICD-9) and Tenth Revision (ICD-10) codes can be used to identify patients with Alzheimer's disease (4). For comparative analyses, it may be important to identify patients with amyloid beta pathology. For the ApoE ε4 status, there may be Current Procedural Terminology (CPT) codes for ApoE testing. However, SDD data would not include the results of such testing. For antithrombotics, claims could be used to identify a subset of patients with prescription anticoagulant or antiplatelet exposure, but not any over-the-counter aspirin exposure. For CAA, per the Boston Criteria version 2.0, the definitive diagnosis is made postmortem and probable/possible diagnoses require brain MRIs (3). Neuroimaging results are not available in the SDD. Although there is an ICD-10 code for CAA, it is not clear how this code is used in clinical practice; it has not been validated, including against the Boston Criteria.

3 EXPOSURES

3.1 Treatment Exposure(s)

The exposure of interest is lecanemab, which will be administered at infusion centers.

3.2 Comparator Exposure(s)

It may be informative to consider the background risk of these outcomes in Alzheimer's disease patients who are untreated or exposed to other FDA approved medications indicated for the treatment of Alzheimer's disease.

3.3 Is Active Risk Identification and Analysis sufficient to identify the exposure of interest?

Yes, once a Healthcare Common Procedure Coding System (HCPCS) code is assigned for lecanemab, the Active Risk Identification and Analysis system will be sufficient to identify lecanemab exposure. Other Alzheimer's disease treatments should be captured in prescription claims via National Drug Codes.

4 OUTCOME(S)

4.1 Outcomes of Interest

The primary outcomes of interest include ARIA-E, ARIA-H, and intracerebral hemorrhage (>1 cm).

4.2 Is Active Risk Identification and Analysis sufficient to assess the outcome of interest?

There are no ICD codes or validated, computable phenotypes for ARIA-E or ARIA-H, which are radiographic findings. However, there are ICD codes that may plausibly be used by providers to capture ARIA. For intracerebral hemorrhage, validated ICD algorithms for intracerebral hemorrhage have been leveraged in past SDD analyses (5). Although there are validated algorithms for intracerebral hemorrhage, the validity may not be applicable to patients with Alzheimer's disease taking amyloid beta-directed monoclonal antibodies. Because there are no ICD codes for ARIA, providers could be coding ARIA-H as intracerebral hemorrhage, making intracerebral hemorrhage codes less specific in this treated, patient population. Additionally, claims cannot restrict to intracerebral hemorrhage by size (i.e., >1 cm). It is important that the outcome of intracerebral hemorrhage should distinguish between ARIA-H and intracerebral hemorrhage >1 cm. Validation of claims codes for these outcomes in patients with Alzheimer's disease is needed. Medical chart review capabilities are not available in the Sentinel Active Risk Identification and Analysis system. Given medical chart review is needed, the Active Risk Identification and Analysis system would be insufficient for assessing any of the primary outcomes of interest in a population of patients with Alzheimer's disease and the defined subpopulations of interest.

5 COVARIATES

5.1 Covariates of Interest

The covariates required for analyses would depend on whether the analysis is addressing the risk of ARIA and intracerebral hemorrhage in the broad, overall population of Alzheimer's disease patients or a specific subpopulation.

To examine the incidence of ARIA and intracerebral hemorrhage in the broad, overall Alzheimer's disease population, covariates of interest include sociodemographics (i.e., age, sex, race, insurance type), clinical characteristics (i.e., comorbidities, disease duration, disease severity, concomitant medications), and healthcare access/utilization (frequency of care, provider type, setting of care).

These covariates will help characterize the population of Alzheimer's disease patients who receive lecanemab outside of clinical trials.

For analyses of risk, especially in the three subpopulations, in addition to the aforementioned covariates, ApoE ε4 status, antithrombotic use, and underlying CAA are also important covariates. There may be interaction and/or effect modification in risk in one subpopulation by the defining features of the other subpopulation(s), requiring capture of these additional covariates (i.e., ApoE ε4 status, antithrombotic use, underlying CAA). For example, the risk of ARIA or intracerebral hemorrhage in patients taking antithrombotics may differ by underlying CAA or ApoE status, thus capture of CAA and ApoE status is important. Also, ApoE ε4 alleles are associated with CAA (6), making ApoE ε4 status a potential confounder for an assessment of associations between CAA and ARIA or intracerebral hemorrhage.

5.2 Is Active Risk Identification and Analysis sufficient to assess the covariates of interest?

Several of the covariates listed above can be captured in claims data (age, sex, race, insurance type, comorbidities, disease duration, concomitant medications, frequency of care, provider type, setting of care). For disease severity, although not directly available in claims, it could possibly be captured through a proxy, such as the Claims-Based Frailty Index (7).

The variables ApoE ε4 status, antithrombotic use, and underlying CAA are critical to defining the subpopulations of interest. For the subpopulation analyses, given possible interaction and/or effect modification in risk in one subpopulation by the defining features of the other subpopulation(s), capture of these covariates is also important. These covariates that would need to be derived from brain MRIs (i.e., evidence of underlying CAA), or genetic testing (i.e., ApoE ε4 status) would not be available in claims data. Consequently, the Active Risk Identification and Analysis system would be insufficient to capture the necessary covariates to define these subpopulations and to address risk in the subpopulation analyses.

The Active Risk Identification and Analysis system would be sufficient to capture covariates for the analysis of the incidence of ARIA and intracerebral hemorrhage in the broad, overall population of Alzheimer's disease patients. Although it would be helpful to know ApoE ε4 status, concomitant antithrombotic use, and underlying CAA for risk analyses, these covariates are not essential in estimating incidence of ARIA and intracerebral hemorrhage in the broad, overall population of patients on lecanemab, irrespective of ApoE ε4 status, concomitant antithrombotic use, and underlying CAA status. Furthermore, for measures of association, capture of these covariates would be important especially if prescribing was differential by these covariates. However, current labeling does not contraindicate use in any of these subpopulations, so it is unknown if these factors would lead to differential prescribing practices and possible confounding. As a result, although these covariates are important for the subpopulation analyses given the potential for interaction and/or effect modification, they are not as critical for the broad, overall population analysis.

6 SURVEILLANCE DESIGN / ANALYTIC TOOLS

6.1 Surveillance or Study Design

The study would require descriptive analysis and covariate adjusted estimates of risk stratified by subpopulations.

6.2 Is Active Risk Identification and Analysis sufficient with respect to the design/analytic tools available to assess the question of interest?

Yes, the Active Risk Identification and Analysis system is sufficient to conduct descriptive analysis, analysis adjusted for multiple covariates, and stratified analysis.

7 NEXT STEPS

On June 23, 2023, a Signal Assessment Meeting was held, which confirmed the determination that the Active Risk Identification and Analysis system in SDD is insufficient to assess the risk of ARIA and intracerebral hemorrhage in 1) a broad, overall population of Alzheimer's disease patients, and 2) the three subpopulations of interest—ApoE ε4 homozygotes, patients with concomitant exposure to antithrombotics, and 3) patients with underlying CAA. Representatives from the Office of Surveillance and Epidemiology (OSE), including the OSE Sentinel Core Team, and the Office of New Drugs, including DN1, were in attendance. The group agreed with the insufficiency determination. Upon traditional approval, DN1 will issue a FDAAA Post-Marketing Requirement (PMR) for two studies with the following draft language:

PMR #4384-5: Conduct a registry-based, prospective, observational study to evaluate clinical safety outcomes among Alzheimer's disease patients treated with lecanemab-irmb, using, for example, the Alzheimer's Network for Treatment and Diagnostics (ALZ-NET) registry, including patients who are ApoE ε4 homozygotes, and/or exposed to antithrombotics, and/or have a diagnosis of, or imaging findings consistent with a high risk for, cerebral amyloid angiopathy. The primary clinical safety outcomes should include amyloid related imaging abnormalities (ARIA)-edema (ARIA-E), and ARIA- hemosiderin deposition (ARIA-H) and any associated clinical symptoms, and intracerebral hemorrhage >1 cm in size. Additional outcomes of interest should also include seizures, anaphylaxis, and death. Baseline characterization of the registry population should include demographic data, diagnosis and stage of disease, ApoE genotype, baseline MRI findings (e.g., microhemorrhages, evidence of cerebral amyloid angiography or other imaging findings consistent with high risk of cerebral amyloid angiography, etc.), other biomarkers that are potential predictors of disease course or adverse outcomes, and prior medications including prior Alzheimer's disease (AD) therapy and antithrombotic therapy. The registry should also collect information on concomitant medications (e.g., antiplatelet and antithrombotic drugs, other AD treatments). When available, the study should provide a comparison of safety outcomes to estimated background rates in an appropriate comparator population.

PMR #4384-6: Use emerging safety data from ongoing studies and published literature, validate administrative claim codes for intracerebral hemorrhage in patients with Alzheimer's disease. The outcome of intracerebral hemorrhage should distinguish between amyloid related imaging abnormalities-hemosiderin deposition (ARIA-H) and cerebral hemorrhage greater than 1 cm. Secondary outcomes of interest include ARIA-edema (ARIA-E) and ARIA-H, seizures, anaphylaxis, and death. For secondary outcomes not well validated, develop algorithms and/or computable phenotypes using data leveraged from PMR 4384-5 and other sources for the outcomes of interest. Describe an approach to identifying an appropriate comparator group with Alzheimer's disease untreated with lecanemab-irmb. Obtain FDA agreement with the outcome algorithm specifications and comparator population prior to proceeding to conducting the retrospective cohort study. Based upon validated algorithms agreed to by the Sponsor and FDA, conduct a comparative retrospective cohort

study using claims data with available medical chart review as needed or electronic health record data to assess clinical safety outcomes in a broad population of Alzheimer's disease patients treated with lecanemab.

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4 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

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07/06/2023 02:14:47 PM

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: June 28, 2023

To: Deniz Erten-Lyons, Clinical Reviewer
Division of Neurology Products (DN1)

E. Andrew Papanastasiou, Regulatory Project Manager, (DN1)

Tracy Peters, Associate Director for Labeling, (DN1)

From: Sapna Shah, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Aline Moukhtara, Team Leader, OPDP

Subject: OPDP Labeling Comments for LEQEMBI™ (lecanemab-irmb), injection, for intravenous use

BLA: 761269/S-001

In response to DN1's consult requests dated January 24, 2023 OPDP has reviewed the proposed product labeling (PI) and Medication Guide for the supplemental BLA submission for LEQEMBI™ (lecanemab-irmb), injection, for intravenous use (Leqembi). This supplement (S001) includes revisions to sections 1 (indication and usage), 2 (dosage and administration), 4 (contraindications), 5 (warnings and precautions), 6 (adverse reactions), 12.2 (pharmacodynamics),12.6 (immunogenicity),14 (clinical studies) and 17 (patient counseling information). In addition, this supplement includes proposed changes to reflect the results of Study 301, which was the confirmatory clinical trial, verifying clinical benefit of Leqembi in patients with Alzheimer's disease.

PI: OPDP's comments on the proposed labeling are based on the draft labeling received by electronic mail from DN1 (E. Andrew Papanastasiou) on June 14, 2023, and are provided below.

Medication Guide: A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed, and comments on the proposed Medication Guide were sent under separate cover on June 28, 2023.

Thank you for your consult. If you have any questions, please contact Sapna Shah at (240) 402-6068 or Sapna.Shah@fda.hhs.gov.

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/s/

SAPNA SHAH
06/28/2023 10:30:15 AM

Clinical Inspection Summary

Date	5/16/2023
From	Cara Alfaro, Pharm.D., Clinical Analyst Phillip Kronstein, M.D., Team Leader Jenn Sellers, M.D., Ph.D. Branch Chief Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations
To	Emilios (Andrew) Papanastasiou, M.S., Pharm.D., Regulatory Project Manager Kevin Krudys, Ph.D., Clinical Reviewer Ranjit Mani, M.D., Team Leader Division of Neurology 1 Office of Neuroscience
NDA #/BLA #	BLA #761269 S-1
Applicant	Eisai, Inc.
Drug	Leqembi (lecanemab-irmb)
NME	No
Proposed Indication	Treatment of early Alzheimer's disease
Consultation Request Date	3/3/2023
Clinical Inspection Summary Goal Date	5/26/2023
Priority/Standard Review	Priority
Action Goal Date	7/6/2023
PDUFA Date	7/6/2023

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Drs. Bolouri, Liss, and Stein were inspected in support of this BLA covering Protocol BAN2401-G000-301. The study appears to have been conducted adequately, and the data generated by these sites appear acceptable in support of the respective indication.

Primary efficacy data, Clinical Dementia Rating-Sum of Boxes (CDR-SB), and key secondary efficacy data, Alzheimer Disease Assessment Scale-Cognitive subscale (ADAS-Cog14) and the Alzheimer's Disease Cooperative Study-Activities of Daily Living Scale for Mild Cognitive Impairment (ADCS MCI-ADL) were verified. Several 1-point discrepancies in the unadjusted ADAS-Cog14 scores were identified in four subjects randomized to lecanemab at Dr. Stein's site, only one involving a timepoint for efficacy analyses (baseline). It is unlikely that a 1-point discrepancy in one baseline unadjusted ADAS-Cog14 score would significantly impact the efficacy analyses for this key secondary efficacy endpoint. Additionally, there was no evidence of under-reporting of adverse events.

II. BACKGROUND

Lecanemab-irmb (Leqembi®) injection for intravenous use was approved on 1/6/2023 for the treatment of Alzheimer's disease under the accelerated approval pathway. Accelerated approval was granted based on the biological surrogate endpoint, reduction in amyloid beta plaques. This accelerated approval included a post-marketing requirement to conduct a confirmatory study to verify the clinical benefit of lecanemab. The sponsor is submitting this efficacy supplement, BLA 761269 S-1, which includes the results of the confirmatory Phase 3 study, Protocol BAN2401-G000-301, to fulfill this post-marketing requirement.

Protocol BAN2401-G000-301

Title: "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" *[Note: BAN2401 is lecanemab]*

Subjects: 1807

Sites: 214 sites; North America (112 [101 in US]), Asia/Pacific (47), Western Europe (47), Australia (7), Eastern Europe (1)

Study Initiation and Completion Dates: 3/27/2019 to 8/25/2022 (Core Study); Open-Label Extension Phase is ongoing

Data Cut-off Date (open-label extension): 4/15/2022

Database Lock: 9/13/2022

This was a double-blind, placebo-controlled, parallel-group study in subjects with Alzheimer's disease (AD). Included were subjects diagnosed with either mild cognitive impairment (MCI) due to AD-intermediate likelihood or mild AD dementia fulfilling the following criteria:

MCI due to AD-intermediate likelihood:

- Meet National Institute of Aging-Alzheimer's Association (NIA-AA) core clinical criteria for MCI due to AD-intermediate likelihood
- Have a global Clinical Dementia Rating (CDR) score of 0.5 and a CDR Memory Box score of $\geq$0.5 at screening and baseline
- Report a history of subjective memory decline with gradual onset and slow progression over the last year before screening, must be corroborated by an informant

Mild AD dementia:

- Meet the NIA-AA core clinical criteria for probable AD dementia
- Have a global CDR sore of 0.5 to 1.0 and a CDR Memory Box score of ≥0.5 at screening and baseline

Other main inclusion criteria were male or female; ≥50 and <90 years of age; MMSE score ≥22 and ≤30 at screening and baseline; if taking approved treatment for AD (e.g. anticholinesterase inhibitors, memantine) dose must be stable for at least 12 weeks prior to baseline; objective impairment in episodic memory as indicated by at least one standard deviation below age-adjusted mean in the Wechsler Memory Scale IV-Logical Memory subscale II (WMS-IV LMII); positive biomarker for brain amyloid pathology as indicated by PET or cerebrospinal fluid (CSF); and have an identified study partner defined as a person able to support the subject for the duration of the study and who spends at least 8 hours per week with the subject.

The study was comprised of 3 phases: Pre-randomization Phase, Randomization Phase, and Open-Label Extension Phase. *The Pre-randomization and Randomization Phases are referred to as the Core Study.*

Pre-randomization Phase (Day -60 to Day -1)
The Pre-randomization Phase was composed of the screening (Visit 1) and baseline (Visit 2) visits. Assessments conducted during the screening visit included but were not limited to labs, apolipoprotein E (*APOE*) status, MMSE, CDR, ECG, and MRI. Assessments conducted during the baseline visit included but were not limited to labs, physical examination, PET imaging, and clinical assessments including MMSE, CDR, ADAS-Cog14.

Randomization Phase (Week 1/Visit 3 to Week 79/Visit 42)
At Visit 3, subjects were randomized (1:1) to one of the following study arms:

- Lecanemab 10 mg/kg intravenous infusion every 2 weeks
- Placebo (normal saline) intravenous infusion every 2 weeks

Randomization was stratified by clinical subgroup (MCI due to intermediate likelihood AD/mild AD dementia), presence or absence of concomitant AD treatment, *APOE4* status, and geographical region.

There were 3 longitudinal sub-studies in this protocol for amyloid PET, CSF biomarker assessments, and tau PET. Participation in these sub-studies was optional and required separate consent.

Subjects who completed the Randomization Phase had the option to enter the Open-Label Extension Phase. Subjects not continuing in this phase had a follow-up visit (Visit 43) 3 months after the last dose of investigational product.

Open-Label Extension Phase (up to 4 years)
Subjects received open-label lecanemab 10 mg/kg intravenous infusion every 2 weeks for up to 4 years, or until lecanemab was commercially available.

The *primary efficacy endpoint* was the change from baseline to 18 months in the Clinical Dementia Rating-Sum of Boxes (CDR-SB), comparing lecanemab to placebo. *Key secondary measures* included the Alzheimer Disease Assessment Scale-Cognitive subscale (ADAS-Cog14) and the Alzheimer's Disease Cooperative Study-Activities of Daily Living Scale for Mild Cognitive Impairment (ADCS MCI-ADL).

Rationale for Site Selection

Clinical sites for BIMO inspections were selected based on risk ranking in the CDER clinical investigator site selection tool (CISST), enrollment, and prior inspections.

III. RESULTS

1. Mohammad R. Bolouri, M.D.
Site #1032
Alzheimer's Memory Center (AMC) Research, LLC
7809 Sardis Road
10801 Monroe Road, Suite 100
Matthews, NC 28105
Inspection Dates: 3/30/2023 – 4/4/2023

At this site for Protocol BAN2401-G000-301, 64 subjects were screened, 20 subjects were randomized, and 16 subjects completed the core study (pre-randomization and randomization phases) and entered the open-label extension phase. Four subjects discontinued the core study due to adverse event (n = 1), withdrawal of consent (n = 2), and "other" – facility lockdown/COVID (n = 1). Subject (b) (6) randomized to lecanemab, withdrew due to the adverse event of amyloid-related imaging abnormality - hemorrhage (ARIA-H) asymptomatic microhemorrhage. Narratives for all of these discontinuations during the core study were included in the BLA submission.

Twelve of the 16 subjects who continued in the open-label extension phase are currently active. Four subjects discontinued the open-label extension phase:

- SAE: COVID-10 pneumonia/death (Subject # (b) (6))
- SAE: Infusion-related reaction (Subject (b) (6))
- SAE: Infusion-related reaction (Subject (b) (6))
- SAE: Symptomatic ARIA-H and ARIA-E (Subject # (b) (6))

Narratives for these discontinuations due to adverse events were included in the 90-day safety update submitted to the BLA.

Signed informed consent forms, dated prior to participation in the study, were present for all subjects who were screened. An audit of the study records for all randomized subjects was conducted. Records reviewed included, but were not limited to, source documents, monitoring documents, IRB/sponsor communications, financial disclosure, test article accountability, inclusion/exclusion criteria, adverse event reports, laboratory results, concomitant medications, protocol deviations, key secondary efficacy data (Alzheimer Disease Assessment Scale-Cognitive subscale [ADAS-Cog14], Alzheimer's Disease Cooperative Study-Activities of Daily Living Scale for Mild Cognitive Impairment [ADCS MCI-ADL]), and primary efficacy data (Clinical Dementia Rating-Sum of Boxes [CDR-SB]).

There was no evidence of underreporting of adverse events. The primary and key secondary efficacy data were entered by site raters into electronic tablets supplied by the vendor, (b) (4) Source data at the site consisted of printed copies from the electronic tablets provided by the vendor, which were verified against sponsor data line listings. No discrepancies were identified for the primary efficacy data, CDR-SB scores, or key secondary efficacy data, ADCS MCI-ADL scores. In the BLA submission, the sponsor had included data line listings for adjusted ADAS-Cog14 scores based on a calculation for two of the sub-score items (word recall and number cancellation) as described in the Statistical Analysis Plan. The source data at the site for the ADAS-Cog14 scores were unadjusted scores. The lack of data line listings for unadjusted ADAS-Cog14 scores was not recognized until after this inspection had been completed; therefore, these data were not verified.

Reviewer comments: This was the first clinical investigator inspection completed for this submission. Due to the unavailability of sponsor data line listings for unadjusted ADAS-Cog14 scores, the data for this key secondary efficacy endpoint could not be verified. This reviewer was unaware of this issue until after the inspection had been completed. The sponsor was asked to provide these data to the other two clinical sites for data verification during the remaining inspections.

Three CDR raters were listed on the study delegation log maintained at the site. Per protocol, CDR raters were not to participate in the medical management of subjects and must be blinded to results of safety assessments, including the safety MRI, clinical laboratory assessments, and adverse events. According to the study delegation log, none of the CDR raters had any other study responsibilities; the third rater (nurse) had one additional delegated task of study drug dispensing.

2. Jonathan Liss, M.D.
Site #1003
Columbus Memory Center
7196 North Lake Drive
Columbus, GA 31909
Inspection Dates: 4/25/2023 – 4/27/2023

At this site for Protocol BAN2401-G000-301, 81 subjects were screened, 38 subjects were randomized, 29 subjects completed the core study (pre-randomization and randomization phases) and 27 entered the open-label extension phase. Nine subjects discontinued the core study due to withdrawal of consent (n = 6), adverse events (n = 2), and "other" described as progression of disease (n = 1). Subject # (b) (6), randomized to placebo, and Subject # (b) (6) (b) (6) randomized to lecanemab, discontinued the core study due to death (undetermined cause). Twenty-three of the 27 subjects who continued in the open-label extension phase are currently active. Four subjects discontinued the open-label extension phase due to withdrawal of consent. Narratives for all of these discontinuations during the core study were included in the BLA submission.

Signed informed consent forms, dated prior to participation in the study, were present for all subjects who were screened. An audit of the study records for all randomized subjects was conducted. Records reviewed included, but were not limited to, source documents, monitoring documents, IRB/sponsor communications, financial disclosure, test article accountability, inclusion/exclusion criteria, adverse event reports, laboratory results, concomitant medications, protocol deviations, key secondary efficacy data (ADAS-Cog14, ADCS MCI-ADL), and primary efficacy data (CDR-SB).

There was no evidence of underreporting of adverse events. Source data for the primary and key secondary efficacy data consisted of printed copies from the electronic tablets provided by the vendor, which were verified against sponsor data line listings. Upon request, the sponsor provided data line listings for unadjusted ADAS-Cog14 scores to the site for data verification (see inspection summary for Site #1032 above). No discrepancies were identified for the primary efficacy data, CDR-SB scores, or key secondary efficacy data, ADAS-Cog14 and ADCS MCI-ADL scores. Three CDR raters were listed on the study delegation log maintained at the site. According to the delegation log, none of the CDR raters had any other study responsibilities.

One protocol deviation was described in the sponsor data listings as an overdose occurring in Subject # (b) (6) at Visit 3 (randomization). The investigational product (IP) dose for this subject, who was randomized to lecanemab, was calculated based on weight in pounds rather than kilograms. Due to this error, this subject received lecanemab 22 mg/kg (1390 mg) instead of 10 mg/kg (630 mg). This error was discovered after the end of the infusion. The sponsor's medical monitor was notified that same day. The subject and spouse were also notified of the error. The subject remained onsite and was monitored for the protocol required four hours. The sponsor required that the subject skip the next scheduled dosing at Visit 4 and return for

Visit 5. The subject returned for an unscheduled study visit the day after the Visit 3 infusion and four days after the Visit 3 infusion for safety evaluation, including clinical labs, physical and neurological examination, EKG, and a pharmacokinetic sample. The subject did not report any adverse events. The subject completed this study and entered the open-label extension phase. The IRB was notified and approved a corrective and preventive action plan (CAPA) that included a two-signature verification process prior to IP dosing. The event of "overdose" was considered a serious event, and the site submitted an SAE form.

Reviewer comments: An IP dosing error occurred in one of 38 randomized subjects. Due to this error, Subject # (b) (6) randomized to lecanemab, received two times the dose intended. The subject did not report any adverse events and continued in the study. The error was reported to the sponsor and IRB, and a CAPA was implemented to prevent recurrence.

3. Lee Stein, M.D.
Site #1020
Neurology Clinic, P.C.
8000 Centerview Parkway
Suite 500
Cordova, TN 38018
Inspection Dates: 4/24/2023 – 4/27/2023

At this site for Protocol BAN2401-G000-301, 96 subjects were screened, 23 subjects were randomized, and 19 subjects completed the core study (pre-randomization and randomization phases) and entered the open-label extension phase. Three subjects discontinued the core study due to withdrawal of consent, and one subject (Subject # (b) (6)) was transferred to Site #1121. Narratives for all of the discontinuations during the core study were included in the BLA submission.

Eighteen of the 19 subjects who continued in the open-label extension phase are currently active. Subject # (b) (6) discontinued the open-label phase due to "subject choice (reported term)/withdrawal by subject (standardized term)". However, the description provided in the sponsor's subject disposition listing (Listing 16.2.1.1) states "subject did not want to continue after the first dose of OLE caused an AE". This subject received the first and only dose of lecanemab in the open-label phase on (b) (6). According to the sponsor's adverse event line listing, the subject experienced an infusion-related reaction considered to be an SAE and lasting 7 days. A narrative for this subject is included in the BLA submission for prior infusion-related reactions but was not updated in the 90-day safety update to include this event.

Reviewer comments: The eCRF for this subject was included in the BLA submission and it appears that the site had chosen "subject choice" for the discontinuation term while also noting that that subject did not continue after the first dose in the open label phase caused an adverse event. This discontinuation should have been categorized as discontinuation due to the adverse event of infusion-related reaction. While there is a narrative for this subject due to past infusion-

related reactions, the narrative was not updated to include this SAE event. The review division may consider requesting more information regarding this SAE to inform safety analyses.

Signed informed consent forms, dated prior to participation in the study, were present for all subjects who were screened. An audit of the study records for all randomized subjects was conducted. Records reviewed included, but were not limited to, source documents, monitoring documents, IRB/sponsor communications, financial disclosure, test article accountability, inclusion/exclusion criteria, adverse event reports, laboratory results, concomitant medications, protocol deviations, key secondary efficacy data (ADAS-Cog14, ADCS MCI-ADL), and primary efficacy data (CDR-SB).

There was no evidence of underreporting of adverse events. Source data for the primary and key secondary efficacy data consisted of printed copies from the electronic tablets provided by the vendor, which were verified against sponsor data line listings. Upon request, the sponsor provided data line listings for unadjusted ADAS-Cog14 scores to the site for data verification (see inspection summary for Site #1032 above). No discrepancies were identified for the primary efficacy data, CDR-SB scores, or the key secondary efficacy data, ADCS MCI-ADL scores. However, discrepancies were identified in the unadjusted ADAS-Cog14 scores for four of 23 randomized subjects (see Table 1).

Table 1. ADAS-Cog14 Data Discrepancies

Subject	Treatment Arm	Visit	ADAS-Cog14 Score (unadjusted)	
			Source Data	Sponsor Data Listing
(b) (6)	Lecanemab	Visit 9/Week 13	25	24
	Lecanemab	Visit 16/Week 27	31	30
		Visit 22/Week 39	36	35
	Lecanemab	Visit 9/Week 13	24	23
	Lecanemab	Visit 2/Baseline	24	23

Reviewer comments: One-point discrepancies were identified for the unadjusted ADAS-Cog14 scores for four of 23 randomized subjects. Only one of these discrepancies involved a timepoint of interest (baseline) for efficacy analyses. The sponsor, however, used adjusted ADAS-Cog14 scores as outlined in their Statistical Analysis Plan. It is not known how discrepancies in unadjusted scores would impact these analyses. It is unlikely, however, that a 1-point discrepancy in a baseline unadjusted ADAS-Cog14 score would significantly impact the efficacy analyses for this key secondary efficacy endpoint.

Three CDR raters were listed on the study delegation log maintained at the site. According to the delegation log, none of the CDR raters had any other study responsibilities.

One eligibility protocol deviation occurred at this site. Inclusion criterion 2 states that MCI subjects must have a CDR global score of 0.5 at screening and baseline. Subject # (b) (6) had

a CDR global score of 0.5 at screening but a score of 1 at baseline. This subject, randomized to lecanemab, received one dose of IP and was lost to follow-up. This protocol deviation was included in the sponsor data line listing.

{See appended electronic signature page}

Cara Alfaro, Pharm.D.
Clinical Analyst
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Phillip Kronstein, M.D.
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CONCURRENCE:

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Jenn Sellers, M.D., Ph.D.
Branch Chief
Good Clinical Practice Assessment Branch
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cc:

Central Document Room/BLA #761269 S-1
Division of Neurology 1/Division Director/Teresa Buracchio
Division of Neurology 1/Deputy Division Director/Emily Freilich (Acting)
Division of Neurology 1/Medical Team Leader/Ranjit Mani
Division of Neurology 1/Clinical Reviewer/Kevin Krudys
Division of Neurology 1/Clinical Reviewer (Safety)/Deniz Erten-Lyons

Division of Neurology 1/Project Manager/Emilios (Andrew) Papanastasiou
OTS/OB/DBI/Statistical Reviewer/Tristan Massie
OSI/Office Director/David Burrow
OSI/Office Deputy Director/Laurie Muldowney
OSI/DCCE/Division Director/Kassa Ayalew
OSI/DCCE/GCPAB/Branch Chief/Jenn Sellers
OSI/DCCE/GCPAB/Team Leader/Phillip Kronstein
OSI/DCCE/GCPAB/Clinical Analyst/Cara Alfaro
OSI/DCCE/GCPAB Program Analyst/Yolanda Patague
OSI/DCCE/GCPAB Program Analyst/Loreto-Corazon Lim

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/

CARA L ALFARO
05/16/2023 10:08:59 AM

PHILLIP D KRONSTEIN
05/16/2023 11:48:00 AM

JENN W SELLERS
05/16/2023 11:59:13 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761269Orig1s001

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 105081

MEETING MINUTES

Eisai Inc.
Attention: Stacie P. O'Sullivan
Director, Global Regulatory Strategy
200 Metro Boulevard
Nutley, NJ 07110

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 (BAN2401).

We also refer to the teleconference between representatives of your firm and the FDA on July 11, 2022. The purpose of the meeting was to discuss the content and format of a proposed Supplemental Biologics License Application (sBLA) for lecanemab.

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

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

Sincerely,

{See appended electronic signature page}

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

Enclosure:

- Meeting Minutes

[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: Pre-sBLA

Meeting Date and Time: July 11, 2022, from 1:00 PM to 2:00 PM ET
Meeting Location: By teleconference

Application Number: IND 105081
Product Name: Lecanemab (BAN2401)
Indication: Alzheimer's disease
Sponsor Name: Eisai
Regulatory Pathway: 351(a)

FDA ATTENDEES

Office of Neuroscience

Billy Dunn, MD	Director, Office of Neuroscience

Division of Neurology 1

Teresa Buracchio, MD	Director, Division of Neurology 1 (DN1)
Laura Jawidzik, MD	Deputy Director (Acting), DN1
Ranjit Mani, MD	Clinical Team Leader, DN1
Kevin Krudys, PhD	Senior Clinical Analyst, DN1
Sally Jo Yasuda, PharmD, MS	Clinical Safety Team Lead, DN1
Natalie Branagan, MD	Clinical Safety Reviewer, DN1
Ami Mankodi, MD	Clinical Reviewer, DN1

Office of Translational Sciences

Kun Jin, PhD	Biostatistics Team Leader
Yifei Zhang, PhD	Clinical Pharmacology Reviewer

Office of Product Quality

Gunter Boekhoudt, PhD	Biopharmaceutics Reviewer

Division of Regulatory Operations for Neuroscience

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

SPONSOR ATTENDEES

Lynn Kramer, MD, FAAN	Chief Clinical Officer, Neurology Business Group (NBG)	Eisai
Shobha Dhadda, PhD	Sr. Vice President, Biostatistics and Clinical Development Operations, NBG	Eisai
Amanda Goodwin	Executive Director, Global Regulatory Strategy, NBG	Eisai
Mark Hodgkinson	Director, Global Regulatory Strategy, NBG	Eisai
Michael Irizarry, MD	Sr. Vice President, Clinical Research, NBG	Eisai
Tsuyoshi Kobayashi	Japan/Asia Regulatory, NBG	Eisai
David Li, PhD	Sr. Director, Biostatistics, NBG	Eisai
Stacie O'Sullivan	Director, Global Regulatory Strategy, NBG	Eisai
Larisa Reyderman, PhD	Vice President, Clinical Pharmacology and Translational Medicine, NBG	Eisai
Chad Swanson, PhD	Executive Director, Clinical Research, NBG	Eisai
Brian Willis, PhD	Sr. Director, Clinical Pharmacology, NBG	Eisai
Jaren Landen, PhD	Early Alzheimer's Disease Head, Neurodegenerative DU (NDU)	Biogen
Lu Zhang, PhD	TA head for NDU and TDU, Global Regulatory, GSRS	Biogen

1.0 BACKGROUND

In this Type B meeting package, the sponsor is seeking the Agency's advice regarding the content and format of a supplemental biologics license application (sBLA) for lecanemab (BAN2401) for the treatment of Alzheimer's disease.

Lecanemab is a humanized IgG_1 monoclonal antibody directed against soluble Aβ aggregate species. Currently, lecanemab is being developed for the treatment of both preclinical and early Alzheimer's disease under this investigational new drug application (IND), which was originally submitted on June 29, 2010.

Lecanemab has been administered primarily by intravenous (IV) infusion in the clinical trials that have been conducted so far. More recently, the development of a subcutaneously-administered formulation of lecanemab was discussed at a Type B meeting (teleconference) that was held with the sponsor on May 6, 2022.

Lecanemab was granted Breakthrough Therapy designation on June 21, 2021, and Fast Track designation on December 20, 2021.

The formal submission of the initial biologics license application (BLA) for lecanemab seeking the approval of that compound for the treatment of early Alzheimer's disease under the accelerated approval pathway was completed on May 6, 2022; that application is currently under review. The efficacy data in support of that initial application are from two clinical studies: primarily from Study BAN2401-GOO1-201 CORE (Study 201 CORE), a completed 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); and also from an ongoing open-label extension to Study 201 CORE (Study 201 OLE; Study 201 OLE Phase). Under that BLA, Studies 201 CORE and Study 201 OLE are to primarily provide evidence that lecanemab reduces brain amyloid on positron emission tomography, an effect that the Agency has already determined as reasonably likely to predict clinical benefit in Alzheimer's disease.

The objective of the currently proposed sBLA is to verify the clinical benefit of lecanemab in support of the full approval of that compound for the treatment of early Alzheimer's disease. The evidence of the clinical benefit of lecanemab is to come primarily from Study BAN2401-G000-301 CORE (Study 301 CORE; CLARITY AD), a currently ongoing, randomized, double-blind, placebo-controlled, parallel-arm study of 18 months duration, whose primary objective is to evaluate the efficacy of BAN2401 in early Alzheimer's disease; this study will also have amyloid and tau positron emission tomographic substudies. That double-blind segment is being followed by an open-label extension (Study 301 OLE) that is to last a maximum of 2 years. Patients with early Alzheimer's disease (mild cognitive impairment due to Alzheimer's disease with intermediate likelihood OR mild dementia due to Alzheimer's disease, both diagnosed according to the 2018 National Institute on Aging-Alzheimer's Association [NIA-AA] criteria) are to be enrolled and randomized in a 1:1 ratio to BAN2401 (10 mg/kg biweekly, administered by intravenous infusion) or matching placebo. Those enrolled will also be required to have an entry Mini-Mental Status Examination (MMSE) score ≥ 22, and elevated brain amyloid that is indicated by either of the following: positron emission tomography using an amyloid-binding ligand, or cerebrospinal fluid t-tau/$A\beta_{42}$. The primary efficacy parameter is the change from baseline to Month 18 in Clinical Dementia Rating Scale – Sum of Boxes (CDR-SB) score. Key secondary efficacy endpoints are the following: change from baseline in amyloid positron emission tomography standard uptake value ratio composite at Month 18; change from baseline in the 14-item Alzheimer's Disease Assessment Scale – Cognitive ($ADAS\text{-}Cog_{14}$) at

Month 18; change from baseline in Alzheimer's Disease Composite Score (ADCOMS) at Month 18; and change from baseline in the Alzheimer's Disease Cooperative Study-Activities of Daily Living-Mild Cognitive Impairment (ADCS-ADL-MCI) score at Month 18. Other clinical efficacy and biomarkers outcomes (including measurement of various biomarkers in plasma and cerebrospinal fluid) are also being evaluated in that study. Safety outcomes are to include adverse events, vital signs, safety laboratory tests, electrocardiograms, physical examinations, suicidality assessments, and safety brain magnetic resonance imaging (MRI). An approach to detecting and managing amyloid-related imaging abnormalities is specified. The primary efficacy analysis will compare the two treatment groups on the primary efficacy parameter, using the Full Analysis Set (consisting of all subjects who receive at least one dose of study medication and who have a baseline efficacy assessment and at least one post-dose efficacy assessment), and a mixed model for repeated measures approach (at a two-sided alpha of 0.05). A hierarchical analysis is planned for the key secondary efficacy endpoints in the following order (at an alpha of 0.05 at each stage): change from baseline in amyloid positron emission tomography standard uptake value ratio composite at Month 18; change from baseline in ADAS-Cog_{14} at Month 18; change from baseline in ADCOMS at Month 18; and change from baseline in ADCS-ADL-MCI at Month 18. Study 301 Core is to be complete at the time of submission of the proposed sBLA for lecanemab.

The proposed sBLA is also to include summary data from the following interventional studies of lecanemab, all of which will be ongoing when the proposed BLA is submitted: Study 301 OLE; Study 201 OLE; Study BAN2401-G000-303 (Study 303; AHEAD 3-45), a study in subjects with preclinical Alzheimer's disease; and Study DIAN-TU-001 which is ongoing in subjects with dominantly inherited Alzheimer's disease.

Other topics covered in this meeting package include, but are not limited to, the content and format of the efficacy, biomarker (fluid- and imaging-based), safety, and pharmacokinetic data and analyses to be included in the proposed sBLA, and the timelines for the submission of those data.

FDA sent Preliminary Comments to Eisai on July 8, 2022.

2.0 DISCUSSION

Question 1: Study 301 Core, the confirmatory study intended to verify the clinical benefit of lecanemab, will evaluate the efficacy and safety of lecanemab in 1795 subjects. Given the size of Study 301, Eisai proposes to submit a supplemental BLA (sBLA) that focuses on the full Clinical Study Report (CSR) for Study 301 Core, along with the following supportive CTD documents:

1. Module 1 documents
2. Module 2.5 Clinical Overview
3. Module 2.7.1 Summary of Biopharmaceutics
4. Module 2.7.2 Summary of Clinical Pharmacology

5. Module 5 Clinical Study Reports (CSRs) as outlined in Question 2

Eisai believes that the documents outlined above, in addition to the CTD documents previously-submitted as part of the accelerated approval BLA (if approved), satisfy the requirements of 21CFR314.50 for the proposed sBLA. Does the Division agree?

FDA Response to Question 1:
You should provide a Summary of Clinical Safety in Module 2 and an Integrated Summary of Immunogenicity in Module 5.

We recognize that there will be an interplay between the original submission under BLA 761269 and the currently proposed sBLA under the same application. The rest of our responses below are based on the assumption that the actions that the Agency takes regarding the currently proposed sBLA will depend on the actions taken by the Agency in response to the original submission under BLA 76126. If an sBLA does not ultimately prove to be the appropriate type of submission for the information you currently seek to include in that same proposed supplemental application, the presentation of the safety data for BLA 761269 will need to be reconsidered.

Discussion:
In addition to a Summary of Clinical Safety and an Integrated Summary of Immunogenicity, the sponsor plans to include an Integrated Summary of Safety in the submission. (b) (4). The Division noted that qualitative summaries from Study 201 should be included with the sBLA submission and that data from Studies 201 and 301 should not be pooled in the sBLA.

Post-Meeting Note:
For ease of Agency review, please provide the tables and figures that support the Summary of Clinical Safety within that document, rather than referring to those tables with links to the individual study reports.

Question 2: In addition to the CTD documents outlined in Question 1, Eisai proposes to submit the following 5 CSRs (or equivalent) in Module 5:

- Study BAN2401-G000-301 Core (full CSR)
  - Sections 1 through 15
  - All Section 14 tables (safety, disposition and efficacy)
  - All Section 16 appendices
- Study BAN2401-G000-301 OLE (synoptic CSR)
  - Section 2
  - All Section 14 tables (safety, disposition and efficacy)
  - All Section 16 appendices
- Study BAN2401-G000-201 OLE (synoptic CSR)
  - Section 2 (methodologies and all safety, disposition)

    - Section 14 tables for safety, disposition
    - All Section 16 appendices except 16.2.3 (patients excluded from the efficacy analysis) and 16.2.6 (individual efficacy response data)
- Study BAN2401-G000-303 (synoptic CSR)
    - Section 2 (methodologies and summary of deaths, discontinuations due to adverse events (AEs) and serious adverse events (SAEs), that do not include amyloid-related imaging abnormalities-edema/effusion (ARIA-E), ARIA-H, skin rash and other hypersensitivity reactions [including infusion related reaction events])
    - Appendix 16.1.1 (protocol and protocol amendments)
    - Appendix 16.2.7 blinded deaths, discontinuations due to AEs and SAE Listings, (please see Question 3)
- DIAN-TU-001 (no CSR)
    - If any subjects are administered lecanemab by the data cut off, appendix 16.2.7 deaths, discontinuations due to AEs, and SAE Listings

Given that the CSRs for Studies 101, 104, and Study 201 Core, and safety listings for Study 004 were submitted to BLA 761269, Eisai does not propose to resubmit these studies. Does the Division agree with the proposed CSRs (or equivalent) for inclusion in the sBLA?

FDA Response to Question 2:

If data for any of the studies submitted under the original BLA for lecanemab (BLA 761269) are to be pooled with data from the studies submitted under the proposed sBLA, the relevant supporting data submitted to BLA 761269 (original submission) should also be submitted to the planned sBLA for lecanemab.

In the proposed sBLA for lecanemab, you should include narratives for deaths, serious adverse events (SAEs), discontinuations due to adverse reactions, and adverse events of special interest, including amyloid-related imaging abnormalities (ARIA) and hypersensitivity.

For each ARIA narrative, please include a table (at the end of that narrative) summarizing findings on each set of magnetic resonance (MR) images, with column headings for the following: visit #, analysis date, study day, finding on MR imaging (i.e., presence and type of ARIA), radiographic severity of ARIA, location of ARIA, radiographic resolution date, and time to resolution.

Attachment 1, appended to the end of this letter, provides comprehensive suggestions regarding the presentation of the safety database in the sBLA. We note that not all of the analyses listed in that attachment may be appropriate for the patient population that is to be the subject of the sBLA; however, you should conduct those analyses that apply to your study population.

If Study 301 OLE, Study 201 OLE, or Study 303 is completed at the time of submission of the proposed sBLA for lecanemab, a full complete study report (CSR), rather than a synoptic CSR, should be submitted for that completed study.

Discussion:
None.

Question 3: Consistent with what was provided on 14 Dec 2021 for the accelerated approval BLA clinical module submission, for ongoing, blinded Study 303 Eisai proposes to submit in a separate sequence, the following:

- Listing of deaths due to AEs related to ARIA-E, ARIA-H, skin rash, and other hypersensitivity reactions (including infusion-related reactions)
- Listing of SAEs related ARIA-E, ARIA-H, skin rash, and other hypersensitivity reactions (including infusion-related reactions)
- Listing of discontinuations due to AEs related to ARIA-E, ARIA-H, skin rash, and other hypersensitivity reactions (including infusion-related reactions)
- Subject narratives and case report forms (CRFs) associated with these events

Does the Division agree?

FDA Response to Question 3:
Your proposal appears acceptable.

Discussion:
None.

Question 4: Eisai proposes the following data cut-offs for ongoing clinical studies, does the Division agree?

1. Study BAN2401-G000-301 OLE: 15 Apr 2022 (7-8 months prior to sBLA submission)
2. Study BAN2401-G000-201 OLE: 15 Apr 2022 (7-8 months prior to sBLA submission)
3. Study BAN2401-G000-303: 15 Apr 2022 (7-8 months prior to sBLA submission)
4. DIAN-TU-001: 15 Apr 2022 (7-8 months prior to sBLA submission)

FDA Response to Question 4:
We recommend that you designate cut-off dates that will allow for the most data that may feasibly be captured for each study.

The dates listed above in Question 4 imply that you plan to submit an sBLA in November or December 2022. Presumably, you plan to submit your proposed sBLA to

an approved application (i.e., your current application, based on your assumption that it will be approved). The user fee goal date for BLA 761269 is January 6, 2023. We request that you clarify your thinking regarding the relationships of your current application's goal data, the intended timing of your sBLA submission, and your proposed data cut-off dates.

Discussion:
The sponsor stated that the proposed sBLA for lecanemab would be submitted after the action is taken for the original BLA for lecanemab that is currently under review, assuming that the original BLA is approved. Additionally, the sponsor noted that most of the data to be included in the proposed sBLA for lecanemab will be provided at the time of the initial sBLA submission, and that the 120-Day Safety Update will contain less than 5% of all the data to be submitted. The Division found the sponsor's proposal to be acceptable.

Question 5: (b) (4) Does the Division agree?

FDA Response to Question 5:
(b) (4) your request is not acceptable. You should submit individual data listings in the study-level CSR.

Discussion:
None.

Question 6: For Study 301 Core, to address recent EMA feedback, Eisai proposes a different statistical testing plan for (1) the US/global and, (2) the EMA. Does the Division have any feedback on the proposed US statistical testing plan, and on the proposed Statistical Analysis Plan in general?

FDA Response to Question 6:
Based on the protocol amendment and updated statistical analysis plan for Study 301 Core that you submitted to the current IND on June 17, 2022, we understand that the statistical testing plans for the US/global and the EMA are no longer different. We have no objection to the statistical analysis plan that you have proposed, but we have the following general comments regarding that plan.

1. Differences in results between the full analysis Set (FAS) and FAS+ analysis populations may be a matter of review along with other possible impacts of the COVID-19 pandemic since the FAS excludes some randomized subjects on account of the pandemic.

2. If the proportion of intercurrent events, such as changes in concomitant medications prescribed for Alzheimer's disease, is not low, the estimand and interpretability of the analysis may be a matter of review.

3. The change in Clinical Dementia Rating Scale-Sum of Boxes (CDR-SB) score could potentially be negative and it is not clear how your log-transformed sensitivity analysis would handle such cases.

Discussion:
The sponsor proposed to add a constant 10 to the change in CDR-SB score before log transformation to account for a potential negative change in that outcome. The Agency commented that adding a large constant before log transformation may reduce the signal and be challenging to interpret. The Agency further added that this issue may be a matter of review.

Question 7: Does the Division agree with: (1) the proposed population PK and PK/PD (exposure-response) analyses for biomarkers, safety (ARIA-E) and efficacy for the sBLA submission as outlined below and detailed in the population PK/PD analysis plan (CPMS-BAN2401-003P-v1); (2) Eisai's proposal to conduct the analysis based on data obtained through 08 Sep 2022 (Study 301 Core database lock); and (3), the proposed dataset submission format?

FDA Response to Question 7:
Your proposed analyses appear acceptable. We also encourage you to evaluate the effect of immunogenicity on pharmacokinetics, pharmacodynamics, and safety in the proposed pharmacokinetic-pharmacodynamic analysis. Information on submitting models and data can be accessed at: https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/model-data-format

Discussion:
None.

Question 8: In accordance with the Draft 2018 Guidance: Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for Center for Drug Evaluation and Research (CDER) Submissions, Eisai proposes to construct the Summary-level Clinical Site Dataset based on the Study 301 Core. Does the FDA agree?

FDA Response to Question 8:
Your proposal appears acceptable.

Discussion:
None.

Question 9: In accordance with the 2020 BIMO Technical Conformance Guide, Eisai

proposes the following analysis populations for BIMO-related deliverables for the submission:

- *CLINSITE dataset: Study 301 Core Safety Population (all subjects who were randomized and received at least one dose of study treatment))*
- *Listings: Study 301 Core Randomized Set*

FDA Response to Question 9:
Your proposal appears acceptable.

Discussion:
None.

Question 10: For Studies 301 Core, 301 OLE, and 201 OLE 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 Study 301 Core and 301 OLE
- SAS programs for creating key safety tables and figures for Study 201 OLE, 301 Core, and 301 OLE
- SAS programs to create the tables and figures for all primary and key secondary efficacy analyses for Study 301 Core and 301 OLE

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

FDA Response to Question 10:
Your proposal appears acceptable.

Discussion:
None.

Question 11: (b) (4) Does the FDA agree?

FDA Response to Question 11:
We do not concur with your request; (b) (4) Note that, if your sBLA application were to receive priority review, you should be prepared to submit a safety update at 90 days after the initial submission rather than at 120 days.

Your safety update should include updated datasets as well as narratives for deaths, SAEs, discontinuations due to AEs, and adverse events of special interest.

Discussion:
The sponsor plans to submit a 120-Day Safety Update to the proposed sBLA for lecanemab as soon as possible, and possibly as early as 90 days, following the initial submission of the sBLA. That update will be based on all safety data obtained up to the date of the initial sBLA submission. The sponsor will also submit an updated Integrated Summary of Safety and Integrated Summary of Immunogenicity together with updated full study reports for ongoing studies. The Division found the sponsor's proposal to be acceptable.

Question 12: In accordance with 21CFR54, Eisai considers Study 301 Core the covered clinical study in the proposed sBLA and as such, plans to include financial certification for all applicable Study 301 Core Investigators. Does the Division agree?

FDA Response to Question 12:
Your proposal appears acceptable.

Discussion:
None.

Question 13: Does the Division agree with the Table of Contents for the proposed sBLA?

FDA Response to Question 13:
Your proposed Table of Contents is acceptable.

Discussion:
None.

ADDITIONAL ITEMS DISCUSSED

1. Proposed upcoming interactions between the sponsor and Agency regarding lecanemab were listed by the sponsor. These were noted by the Agency.

2. The sponsor indicated that topline clinical data for the CLARITY AD study are expected to be available by the end of September 2022: these are to include primary and key secondary efficacy data, as well as key safety data (i.e., the incidence of each type of ARIA). The database for the CLARITY AD study is expected to be locked on or about September 8, 2022.The sponsor plans to issue a brief press release once topline clinical data for the CLARITY AD study become available, and would like to share that press release and those topline data with the Agency either by email or at a teleconference; the Agency found that proposal to be acceptable.

3.0 ADDITIONAL INFORMATION

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.

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End-of-Phase-2 (EOP2) meeting. In the absence of an EOP2 meeting, refer to the draft guidance below. The iPSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The iPSP should be submitted in PDF and Word format. Failure to include an Agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the draft guidance for industry *Pediatric Study Plans:*

Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans.[2] In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email Pedsdrugs@fda.hhs.gov. For further guidance on pediatric product development, please refer to FDA.gov.[3]

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information[4] and Pregnancy and Lactation Labeling Final Rule[5] websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential.
- Regulations and related guidance documents.
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

Pursuant to the PLLR, you should include the following information with your application to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. The application should include a review and summary of the available published literature regarding the drug's use in pregnant

[2] When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.
[3] https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development
[4] https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information
[5] https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule

and lactating women and the effects of the drug on male and female fertility (include search parameters and a copy of each reference publication), a cumulative review and summary of relevant cases reported in your pharmacovigilance database (from the time of product development to present), a summary of drug utilization rates amongst females of reproductive potential (e.g., aged 15 to 44 years) calculated cumulatively since initial approval, and an interim report of an ongoing pregnancy registry or a final report on a closed pregnancy registry. If you believe the information is not applicable, provide justification. Otherwise, this information should be located in Module 1. Refer to the draft guidance for industry *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format*.

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

ABUSE POTENTIAL ASSESSMENT

Drugs that affect the central nervous system, are chemically or pharmacologically similar to other drugs with known abuse potential, or produce psychoactive effects such as mood or cognitive changes (e.g., euphoria, hallucinations) need to be evaluated for their abuse potential and a proposal for scheduling will be required at the time of the NDA submission [21 CFR 314.50(d)(5)(vii)]. For information on the abuse potential evaluation and information required at the time of your NDA submission, see the guidance for industry *Assessment of Abuse Potential of Drugs*.[6]

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the items described in the draft guidance for industry, *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions,* and the associated conformance guide, *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications,* be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA ORA investigators who conduct those inspections. This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

Please refer to the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical*

[6] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

Specifications.[7]

Attachment 1

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

Datasets:

1. Each individual subject should be assigned a single unique subject identifier across the entire application (e.g., including open label extensions of the trials). Include the unique subject identifier in the ISS and individual studies' datasets.
2. Submit datasets for all Phase 1, Phase 2, Phase 3 studies (including open label extension studies), including the Phase 2 and 3 studies performed for indications other than the one proposed for this application.

For additional guidance refer to the FDA webpage on Study Data Standards Resources.

General Submission Contents:

1. Follow the requirements noted in 21CFR 314.50 (d)(5)(vi), Summary of Safety Information and the Guideline for the Format and Content of the Clinical and Statistical Sections of an Application
2. Provide an assessment of safety as per the FDA Guidance for Industry: Premarketing Risk Assessment
3. Include a copy of each clinical study protocol as well as each amended protocol. Provide a list of the inclusion and exclusion criteria for each of the studies, including those introduced as part of protocol amendments. Please submit all versions of the protocols (and Statistical Analysis Plan) and the date when changes were implemented. Please ensure that a Summary of Changes for each version is included.
4. In addition to the comprehensive analyses performed for the pivotal trials, the ISS should also comprehensively integrate safety analyses for all other study group pools for treatment-emergent adverse events (TEAEs), deaths, serious adverse events, discontinuations for TEAEs, TEAEs of special interest, subgroups, and vital sign/laboratory/ECG measurements.
5. Submit a table detailing all of the tables and figures featured in the clinical efficacy and safety sections of the application. The table should contain the following:
   a. Title of the table or figure in the application
   b. A hyperlink to the location of the table or figure with page number
   c. A hyperlink to the SAS code used to create the table or figure (including information regarding the datasets that were used)

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

6. Format the tables of the ISS according to examples in FDA's Reviewer Guidance – Conducting a Clinical Safety Review of a New Product Application and Preparing a Report on the Review.
7. Include active hyperlinks from the lists of references to the referenced article.
8. Provide DSMB meeting minutes (including any data/slides presented). For those meetings that were cancelled or meetings where no minutes were taken, please include a place holder for that meeting noting such and signed by a member of the clinical team. Please also ensure that these packages come with a table of contents and are bookmarked by date.
9. Include information regarding important regulatory actions in other countries and foreign labeling (translated, if applicable).
10. Submit an annotated version of the pre-BLA meeting minutes that include hyperlinks, when applicable, to the analysis and/or documents requested.

Adverse events:

1. Follow the coding rules for MedDRA in the ICH-endorsed "MedDRA Term Selection: Points to Consider" document accessible at MedDRA
2. For each of the studies, the submitted datasets should contain both the verbatim terms and the MedDRA coding with all levels of the MedDRA hierarchy. For each adverse event, MedDRA coding should be provided for the primary MedDRA path.
3. Provide a summary table of the original AE coding dictionaries that were used in each of the trials.
4. The preparation of the adverse event dataset for the ISS should include MedDRA Preferred Terms from a single version of MedDRA.
5. Ensure that all adverse events are presented, and not only events deemed "drug-related."
6. Provide a table of treatment-emergent adverse events reported in ≥ 2% of subjects (after rounding) in any drug treated dose group (and greater than placebo) sorted by MedDRA SOC (in alphabetical order) and then by MedDRA Preferred Term.
7. Provide a table which summarizes the outcomes of all pregnancies. Provide a table which summarizes all known adverse events in subject offspring.

Narratives and Case Report Forms (CRFs):

1. Provide narratives and case report forms for deaths, adverse events leading to drug discontinuation, SAEs, pregnancies, and AEs of special interest. You should be prepared to supply any additional CRFs or narratives with a rapid turnaround upon request. Narratives should be integrated. For subjects who had more than one event requiring a narrative (whether in the same trial or in the core study and an extension) present a single narrative (rather than separate narratives for the various events).

2. Include a word file (and excel spreadsheet) that indicates those subjects for whom you submitted a case report form and/or narrative. This file should include an indicator for whether each item was submitted and the reason why it was submitted along with hyperlinks to the narrative and CRF.
3. Provide reports for any autopsies conducted during any of the studies.
4. Provide a line listing, narrative, and case report form for all subjects who fit the Hy's Law laboratory criteria.
5. Note that CRFs should include all clinical documents collected about the patient regardless of whether you label them "CRFs", e.g., Medwatch/CIOMS forms, event fax coversheets, SAE or event worksheets, narrative worksheets, data queries, etc.
6. Provide a tabular listing of all subjects with all discontinuations, sorted by reason. The table should include columns for study number, treatment group, unique subject ID, primary reason for drug or study discontinuation. For reasons including Lost to follow-up, Other, Physician/investigator decision, Withdrew consent, and Patient decision, provide more specific information regarding the discontinuation. The Division may want to request selected narratives/CRFs from some of these patients, but they do not need to be submitted at the time of the initial NDA/BLA submission.
7. Narrative summaries should provide a complete synthesis of all available clinical data and an informed discussion of the case. The narratives should be comprehensive enough for the reader to come to a reasonable conclusion regarding the subject and the adverse event. The following items should be included (but not limited to):
    a) Patient age and gender
    b) Adverse event onset and stop dates (presented as relative Study Day number)
    c) Signs and symptoms related to the adverse event being discussed
    d) An assessment of the relationship of exposure duration to the development of the adverse event
    e) Pertinent medical history
    f) Concomitant medications with start dates relative to the adverse event
    g) Pertinent physical exam findings
    h) Any abnormal vital sign measurements
    i) Pertinent test results (e.g., lab data, ECG data, procedures, biopsy data, autopsy results)
    j) Discussion of the diagnosis as supported by available clinical data
    k) For events without a definitive diagnosis, a list of the differential diagnoses
    l) Treatment provided
    m) Re-challenge results (if performed)
    n) Outcomes and follow-up information

Laboratory and Vital Sign Measurements:

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

2. Provide the normal reference ranges for every laboratory value.
3. Clearly list the normal values, as well as the thresholds for analysis of outliers, for outlier analyses of laboratory data, vital signs, and ECG data.
4. When possible, use the latest version of the National Institutes of Health (NIH) Common Terminology Criteria for Adverse Events (CTCAE) for toxicity grades and shift analyses.
5. Report the number and percentage of subjects with at least one post-treatment vital sign measurement meeting any of these criteria:
   - Systolic Blood Pressure: <90 mmHg, >140 mmHg, >160 mmHg
   - Diastolic Blood Pressure: <50 mmHg, >90 mmHg, >100 mmHg
   - Pulse Rate: <60 bpm, >100 bpm
   - Body Weight: decrease of ≥7% from baseline and increase of ≥7% from baseline
   - Temperature: >38.0 °C, <36.0 °C
   - Respiratory rate: <12 breaths/min, > 20 breaths/min
6. Summarize the protocols for collecting ECG data. Summarize the frequency of post-treatment QTc >450 ms, >480 ms, and >500 ms.

Other requests:

1. Patient profiles
   Submit individual patient profiles containing all laboratory and other study results in a single place for each patient. Provide this information for patients who died, had a serious adverse event, discontinued from the trial due to an adverse event, or had a medically significant event for which a narrative is submitted. Include all the information recorded for that patient, including but not limited to:
   a) Age
   b) Sex
   c) Dates of screening, randomization and starting therapy
   d) Whether the patient completed or did not complete the study, with dates and reason for withdrawal
   e) Adverse events (reported term, preferred term, start and stop date [with relative study day], seriousness, outcome, whether it resolved or not and action taken with drug)
   f) Prior medications and concomitant medications with dates of start and end
   g) Vital signs and laboratories, sorted by date, with reference ranges *
   h) Autopsy reports for all deaths. (If an autopsy report is not available, explicitly state this.)
   i) Full reports for radiologic studies, ECG, MRI, pathology results, special studies and procedures with dates and reference ranges
   j) Provide relevant results obtained outside of clinical trial visits, including those obtained during hospitalization or emergency room visits, in each patient file. Also include baseline study results.

k) For patients who had IND safety report(s), include dates when the initial and follow up safety reports were submitted.

Create a PDF file for each patient and a table of contents with links to each assessment for each patient.

2. Please submit for Division comments an example narrative from a patient who had more than one serious adverse event and participated in the controlled and extension studies prior to submitting your NDA.
3. We request that you submit a sample integrated summary of safety datasets (with data definition file) for Division comments prior to submitting the NDA. This process could help to identify and resolve any potential issues of navigability or interpretability that could impact the review of your application.

6.0 ATTACHMENTS AND HANDOUTS

Attached is the handout provided by Eisai and presented at the July 11, 2022, teleconference.

9 Page(s) 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/

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