FDA Briefing Document

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Drug name: lecanemab-irmb

Applicant: Eisai Inc.

Peripheral and Central Nervous System (PCNS) Drugs Advisory Committee Meeting

June 9, 2023

Division of Neurology 1/Office of Neuroscience

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Glossary

Aβ	amyloid beta
AC	Advisory Committee
AD	Alzheimer's disease
ADAS-Cog	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 Mild Cognitive Impairment
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
BD	Briefing Document
BRF	Benefit-Risk Framework
CAA	Cerebral amyloid angiopathy
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDTL	Cross-Discipline Team Leader
CDR	Clinical Dementia Rating
CDR-SB	Clinical Dementia Rating Sum of Boxed
COVID-19	coronavirus disease 2019
CSR	clinical study report
EQ-5D-5L	European Quality of Life-5 Dimensions 5 Level version
FAS	full analysis set
FDA	Food and Drug Administration
GFAP	glial fibrillary acidic protein
IA	integrated assessment
IV	intravenous
MCI	mild cognitive impairment
MMRM	mixed-effects model repeated measures
MMSE	Mini-Mental State Examination

MRI	magnetic resonance imaging
NIA-AA	National Institute of Aging-Alzheimer's Association
NfL	neurofilament light chain
PD	pharmacodynamics
PMR	postmarketing requirement
PET	positron emission tomography
p-tau 181	phosphorylated tau at residue 181
QOL-AD	Quality of Life in Alzheimer's Disease
REMS	risk evaluation and mitigation strategy
RPM	Regulatory Project Manager
SAP	Statistical Analysis Plan
SD	standard deviation
SUVR	standard uptake value ratio
t-tau	total tau
vMRI	volumetric magnetic resonance imaging

1 Executive Summary/Draft Points for Consideration by the Advisory Committee

1.1 Purpose/Objective of the AC Meeting

The FDA is convening this Advisory Committee (AC) meeting to discuss whether the data from the Phase 3 Study 301 (CLARITY AD) confirm the clinical benefit of lecanemab for the treatment of Alzheimer's disease. The evaluation of benefit-risk for lecanemab in Alzheimer's disease will also be discussed.

1.2 Context for Issues to Be Discussed at the AC

Alzheimer's disease (AD) is an irreversible and progressive neurodegenerative disease that affects memory, thinking, and behavior, and is ultimately fatal. AD is the most common cause of dementia among older adults and is the sixth leading cause of death in the United States. While the specific causes of AD are not fully known, the disease is characterized by changes in the brain, including amyloid beta plaques and neurofibrillary tangles, which precede clinical symptoms.

Currently approved treatments for AD include the cholinesterase inhibitors donepezil, rivastigmine, and galantamine, and the N-methyl-D-aspartate receptor antagonist, memantine. These treatments do not target the underlying pathology of AD and their beneficial effects are modest and transitory.

Aducanumab and lecanemab are amyloid beta (Aβ) directed antibodies approved under the accelerated approval pathway based on the observed reduction of amyloid beta plaque quantified using positron emission tomography (PET) imaging. Both aducanumab and lecanemab are indicated for the treatment of AD and the labeling states that treatment should be initiated in patients with mild cognitive impairment (MCI) or mild dementia stage of disease, the population in which treatment was studied in clinical trials. 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. Specifically, accumulated evidence has established that a robust reduction of brain amyloid plaque to levels consistent with a negative PET scan is associated with a reduction in clinical decline over 18 months of approximately 20% to 40% on clinical outcome assessments of cognition and function. These data support the use of reduction of amyloid plaques on PET as a surrogate endpoint reasonably likely to predict clinical benefit.

Eisai Inc. (Applicant) received accelerated approval for lecanemab (trade name Leqembi) on January 6, 2023. As part of the accelerated approval, the Applicant was required to conduct a postmarketing clinical trial verifying and describing the anticipated clinical benefit of lecanemab. The results of the confirmatory study (Study 301) were submitted January 6, 2023 and are the focus of this meeting.

1.3 Brief Description of Issues for Discussion at the AC

On January 6, 2023, the Applicant submitted a supplemental Biologics License Application (sBLA) for lecanemab, a monoclonal antibody directed against aggregated forms of amyloid beta, for the treatment of AD. In support of the proposed indication and to fulfill the postmarketing requirement to verify the clinical benefit of lecanemab for the treatment of AD, the Applicant submitted results of Study 301 (CLARITY AD). Study 301 was a multicenter, randomized, double-blind, placebo-controlled, parallel-group study in patients with MCI due to AD or mild AD dementia. 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 lecanemab 10 mg/kg biweekly in a 1:1 ratio

in the placebo-controlled period. The primary endpoint was the change from baseline in the Clinical Dementia Rating - Sum of Boxes (CDR-SB) at 18 months of treatment. 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. Study 301 met its prespecified primary endpoint, demonstrating a statistically significant treatment effect in the lecanemab treatment arm compared to placebo (-0.45[-27%], p=0.00005). Statistically significant treatment effects were also observed for all multiplicity-controlled secondary endpoints.

The main safety signals associated with the use of monoclonal antibodies directed against aggregated forms of beta amyloid, including lecanemab, are amyloid related imaging abnormalities (ARIA), cerebral hemorrhage, and infusion-related reactions and hypersensitivity. The prescribing information for lecanemab currently describes ARIA and provides monitoring and dose management guideline in the Warnings and Precautions Section 5.1 and in Section 2.3.

ARIA is classified 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. Microhemorrhage and superficial siderosis, as well as mild focal edema, can occur spontaneously in patients with Alzheimer's disease in the absence of treatment with amyloid targeting therapies and may be related to underlying amyloid burden or cerebral amyloid angiopathy (CAA); these are usually observed as incidental findings on MRI. In the setting of treatment with monoclonal antibodies directed against aggregated forms of beta amyloid, ARIA-H generally occurs in association with an occurrence of ARIA-E. ARIA-H of any cause (sporadic or drug-related) and ARIA-E can occur together. ARIA 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 presence of the ApoE E ε4 allele increases the risk of ARIA, with greater risk observed in homozygotes than heterozygotes. The use of antithrombotic medication, particularly, anticoagulation therapy, may increase the risk for cerebral hemorrhage in patients taking lecanemab.

Consistent with the currently approved prescribing information for lecanemab, the primary safety issues identified in Study 301 are ARIA, cerebral hemorrhage, and infusion-related reactions and hypersensitivity, including an anaphylactic reaction. In lecanemab treated patients the incidence of ARIA-E was 13% and the risk of ARIA-H was 17%. The risk of ARIA is increased in ApoE ε4 carriers. The risk of cerebral hemorrhage is increased in patients exposed to anticoagulant medications. Two deaths occurred in subjects who had cerebral hemorrhage after treatment with lecanemab and 1 death occurred in a patient with a possible cerebrovascular accident and severe ARIA-E and ARIA-H. Uncertainty regarding the role of lecanemab in these cases includes the role of concomitant medications, possible contribution of ARIA, the possible presence of cerebral amyloid angiopathy and related vasculitis and its role in such events. Treatment emergent adverse events that occurred in at least 10% of subjects treated with lecanemab and at least 2% higher than placebo were infusion related reactions (26%), ARIA-H microhemorrhages (14%), ARIA-E (13%), and headache (11%).

The safety data from Study 301 generally appears to be consistent with the approved prescribing information for lecanemab. The current prescribing information for lecanemab includes a warning for the risk of ARIA and provides recommendations for monitoring and dose management guidelines. It also describes the increased risk of ARIA in ApoE ε4 homozygotes compared to heterozygotes and noncarriers, and the need to exercise additional caution when considering the administration of antithrombotics or a thrombolytic agent with lecanemab.

An unanswered question is whether the risk of serious outcomes from ARIA are increased in subjects with underlying CAA, noting that there is a substantial overlap between individuals who carry the ApoE ε4 allele and have CAA pathology and that ApoE ε4 homozygotes have been found to have a greater severity of CAA pathology at autopsy.[1][2] 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 this disorder difficult and limits the ability 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 potential for these risks needs to be considered in the benefit-risk discussion between prescribers and patients/caregivers when making the decision to initiate therapy.

The Agency seeks input from the committee on whether the efficacy data from Study 301 confirm the clinical benefit of lecanemab in the treatment of AD, and whether the benefit-risk assessment supports the traditional approval of lecanemab.

1.4 Draft Points for Consideration

- Consider whether results from the Study 301 (CLARITY AD) confirm the clinical benefit of lecanemab in the treatment of AD.
- Consider the overall benefit/risk assessment of lecanemab for the treatment of Alzheimer's disease. Additionally, consider the following subgroups in your assessment:
  - ApoE ε4 homozygotes
  - Patients with cerebral amyloid angiopathy
  - Patients requiring concomitant treatment with anticoagulant agents

2 Introduction and Background

2.1 Background of the Condition/Standard of Clinical Care

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

[1] Greenberg SM, Bacskai BJ, Hernandez-Guillamon M, Pruzin J, Sperling R, van Veluw SJ. Cerebral amyloid angiopathy and Alzheimer disease - one peptide, two pathways. Nat Rev Neurol. 2020 Jan;16(1):30-42. doi: 10.1038/s41582-019-0281-2. Epub 2019 Dec 11. PMID: 31827267; PMCID: PMC7268202.

[2] 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

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 6.2 million Americans aged 65 and older are currently living with Alzheimer's disease dementia, and the number is projected to reach over 12 million by 2050, in the absence of interventions to prevent or slow the disease.[3]

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 has been proposed to be a 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.[4] Based on these findings, National Institute on Aging – Alzheimer's Association (NIA-AA) research criteria have been 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.[5] 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, and the N-methyl-D-aspartate antagonist memantine. Aducanumab and lecanemab are 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 AD. 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 AD.

2.2 Pertinent Drug Development and Regulatory History

Lecanemab (previously BAN2401) is a humanized immunoglobulin gamma 1 (IgG1) monoclonal antibody directed against aggregated soluble and insoluble forms of amyloid beta. The Applicant's proposed indication is as a disease-modifying 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.

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[3] Alzheimer's Association, 2021, 2021 Alzheimer's Disease Facts and Figures, Special Report: Race, Ethnicity and Alzheimer's in America. https://www.alz.org/media/Documents/alzheimers-facts-and-figures.pdf

[4] Vermunt, L, SAM Sikkes, A van den Hout, R Handels, I Bos, WM van der Flier, S Kern, PJ Ousset, P Maruff, I Skoog, FRJ Verhey, Y Freund-Levi, M Tsolaki, AK Wallin, MO Rikkert, H Soininen, L Spiru, H Zetterberg, K Blennow, P Scheltens, G Muniz-Terrera, PJ Visser, for the Alzheimer Disease Neuroimaging Initiative, AIBL Research Group, ICTUS/DSA study groups, 2019, Duration of Preclinical, Prodromal, and Dementia Stages of Alzheimer's Disease in Relation to Age, Sex, and APOE Genotype, Alzheimer's & Dementia, 15:888-898.

[5] Jack, CR Jr., DA Bennet, K Blennow, MC Carrillo, B Dunn, SB Haberlein, DM Holtzman, W Jagust, F Jessen, J Karlawish, E Liu, JL Molinuevo, T Montine, C Phelps, KP Rankin, CC Rowe, P Scheltens, E Siemers, HM Snyder, and R Sperling, 2018 Apr, NIA-AA Research Framework: Toward a Biological Definition of Alzheimer's Disease, Alzheimers Dement, 14(4);535-562.

Lecanemab (trade name Leqembi) received accelerated approval on January 6, 2023, based on reduction in amyloid beta plaques observed in the dose regimen-finding Study 201. At a September 2021 Type B Meeting, the FDA agreed that the ongoing Study 301 could serve as the confirmatory clinical trial to verify the clinical benefit of lecanemab. During the course of Study 301, the Applicant proposed modifications to the study and analysis population in response to the potential impact of the COVID-19 pandemic. The FDA agreed with the Applicant's plan to increase enrollment in the study and noted that their plan to exclude some randomized patients based on site location and randomization date would be a matter of review. In response to a proposal from the Applicant at a December 2021 Type B Meeting, the FDA cautioned against prioritizing the ApoE ε4 population in the sequence of objectives. An efficacy supplement containing the results of Study 301 was submitted on January 6, 2023.

3 Overview of Efficacy and Safety

3.1 Clinical Efficacy Assessment

3.1.1 Sources of Data for Efficacy

The Applicant submitted Study 301 (CLARITY AD) as the confirmatory study to verify and describe the clinical benefit of lecanemab.

Design

Study 301 was a multicenter, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of lecanemab in patients with mild cognitive impairment (MCI) due to AD or mild AD dementia. The primary objective of the study was to determine the superiority of lecanemab compared with placebo on the change from baseline in the Clinical Dementia Rating-Sum of Boxes (CDR-SB) at 18 months of treatment.

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.

A total of 235 centers across 13 countries in North America, Europe, Australia, and Asia enrolled patients into the trial.

Population

Patients fulfilled clinical criteria for either MCI due to AD or mild AD dementia as defined by the 2011 National Institute of Aging-Alzheimer's Association (NIA-AA) framework[6,7] and were required to have evidence of brain Aβ pathology by either visual read of a positron emission tomography (PET) scan or

[6] Albert, MS, ST DeKosky, D Dickson, B Dubois, HH Feldman, NC Fox, A Gamst, DM Holtzman, WJ Jagust, RC Petersen, PJ Snyder, MC Carrillo, B Thies, and CH Phelps, 2011, The Diagnosis of Mild Cognitive Impairment due to Alzheimer's Disease: Recommendations from the National Institute on Aging-Alzheimer's Association Workgroups on Diagnostic Guidelines for Alzheimer's Disease, Alzheimers Dement., 7(3): 270-279.

[7] McKhann, GM, DS Knopman, H Chertkow, BT Hyman, CR Jack Jr., CH Kawas, WE Klunk, WJ Koroshetz, JJ Manly, R Mayeux, RC Mohs, JC Morris, MN Rossor, P Scheltens, MC Carrillo, B Thies, S Weintraub, and CH Phelps, 2011, The Diagnosis of Dementia due to Alzheimer's Disease: Recommendations from the National Institute on Aging-Alzheimer's Association Workgroups on Diagnostic Guidelines for Alzheimer's Disease, Alzheimers Dement., 7(3):263-269.

CSF assessment of t-tau/$A\beta_{1-42}$. Patients had a baseline mini-mental state examination (MMSE) score of 22 to 30 (inclusive) and a CDR global score of 0.5 or 1.0 with a Memory Box score of 0.5 or greater.

Randomization was stratified by clinical subgroup (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 patients enrolled in the study were to be in the MCI due to AD subgroup.

Endpoints

Primary Efficacy 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 the 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 patient 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 Efficacy Endpoints

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 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 AD. 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 AD.

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[8] 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 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 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

[8] Klunk, WE, RA Koeppe, JC Price, TL Benzinger, MD Devous Sr., WJ Jagust, KA Johnson, CA Mathis, D Minhas, MJ Pontecorvo, CC Rowe, DM Skovronsky, and MA Mintun, 2015, The Centiloid Project: standardizing quantitative amyloid plaque estimation by PET, Alzheimers Dement., Jan;11(1):1-15.e1-4

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 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. In an attempt to address potential missed doses due to the COVID-19 pandemic, the FDA FAS was similar to the FAS+, but excluded patients 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).

3.1.2 Disposition, Demographics, and Baseline Characteristics

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. All patients who were randomized received at least one dose of study drug. Of the 1795 patients randomized, 140 patients (15.6%) receiving placebo and 169 patients (18.8%) receiving lecanemab discontinued from the study. The distribution of the reasons for discontinuation between the arms was similar with the exception of more patients in the lecanemab treatment arm discontinuing the study to adverse events (5.7%) compared to placebo (3.1%). Only 16 patients in the study discontinued for reasons related to COVID-19.

Due to disruptions in study drug administration during the peak of the COVID-19 pandemic, the Applicant defined the FDA FAS analysis set with the intention of excluding patients who may have missed consecutive lecanemab doses. Compared to the FAS+ population, a total of 68 patients (26 in the lecanemab treatment arm and 42 in the placebo arm) from 19 sites were excluded. Of the 26 excluded patients in the lecanemab treatment arm, 16 did not have any missed doses due to COVID-19 and only 3 had 3 or more doses missed due to COVID-19.

Baseline demographic and disease characteristics were reasonably balanced between the treatment groups (Table 1) and reflect a population early in the course of AD. Overall, 52% of patients in the FAS+ set were enrolled in the United States. Most patients (53%) were receiving concomitant medications for AD and 3% reported receiving prior treatment with AD medication.

Table 1. Baseline Demographics and Disease Characteristics, FAS+ Population, Study 301

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%)

Demographic or Disease Characteristics	Placebo N=875 n(%)	Lecanemab N=859 n(%)	Total N=1734 n(%)
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%)
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)
Abbreviations: AD, Alzheimer's disease; CDR, Clinical Dementia Rating; FAS+, full analysis set; MCI, mild cognitive impairment; MMSE, mini-mental state examination; SD, standard deviation

3.1.3 Efficacy Results

Primary Efficacy 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.

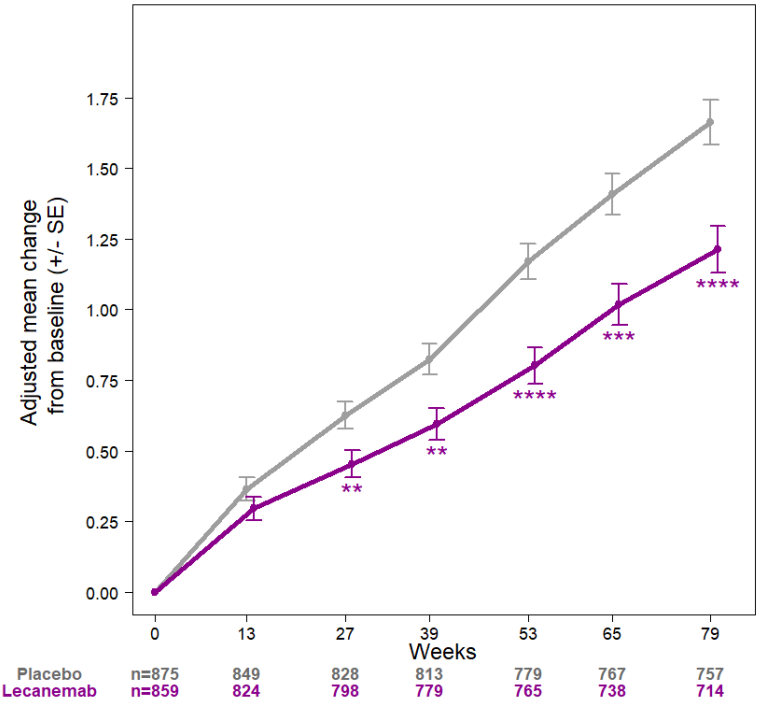
Table 2. Primary Endpoint Analysis, FAS+ Population, Study 301

Parameter	Placebo (N=875)	Lecanemab (N=859)
Baseline CDR-SB		
n	875	859
Mean	3.22	3.17

Parameter	Placebo (N=875)	Lecanemab (N=859)
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

Twenty two (2.5%) placebo and 39 (4.3%) lecanemab patients had no post-baseline efficacy assessments and were therefore not in the FAS+ (or FAS FDA population on which the primary analysis was based). There were 8 deaths in the placebo arm and 7 deaths in the lecanemab arm in the ITT population by Week 79, of which 5 and 7, respectively, were in the FAS+ population. Relying on the observed CDR-SB even in cases of these known bad outcomes of death before Week 79 in the primary analysis could potentially cause bias in the primary analysis, but the proportion of deaths is low for any corresponding bias to be small.

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 in 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 patient'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 patient's treatment group based on occurrence of an ARIA event.

Secondary Clinical Endpoints

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 (Table 3). 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 3. 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	707	-5.500	676	2.016 (-37%)	p<0.00001
ADCOMS	749	0.214	708	-0.050 (-24%)	p=0.00002

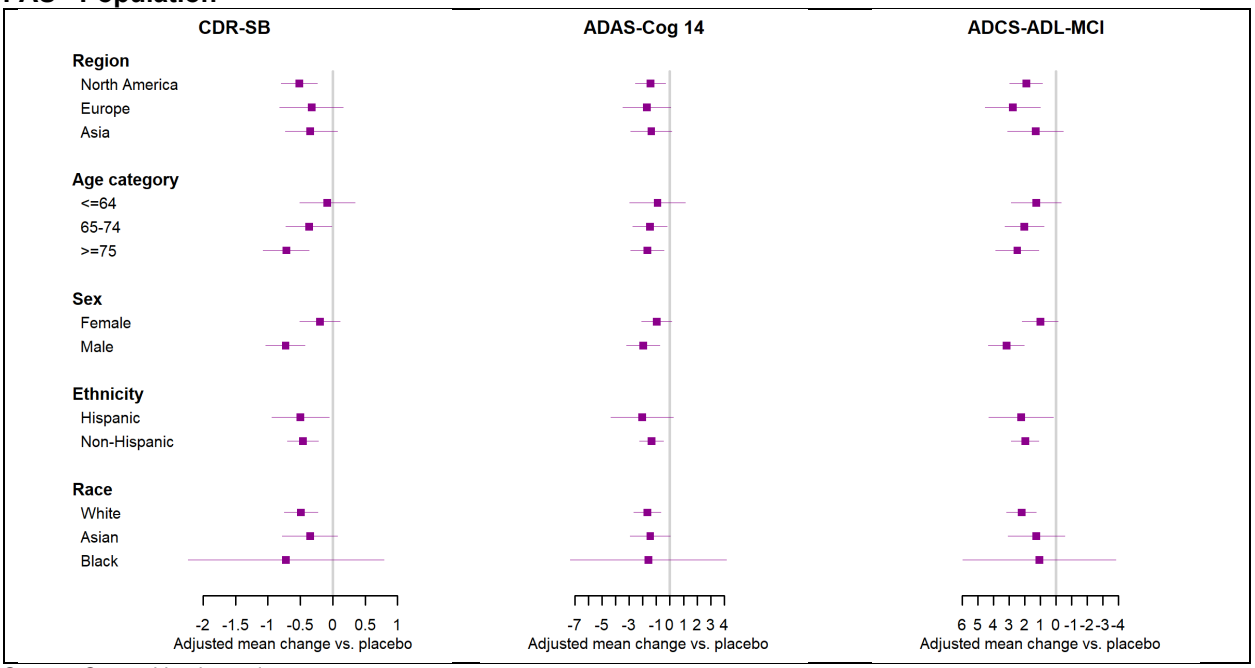
Source: Tables 14.2.2.2.2, 14.2.2.3.2, and 14.2.2.4.2 in Study 301 CSR
Abbreviations: ADAS-Cog 14, 14-item Alzheimer's Disease Assessment Scale - Cognitive Subscale; ADCOMS, Alzheimer's Disease Composite Score; ADCS-ADL-MCI, Alzheimer's Disease Cooperative Study - Activities of Daily Living Scale for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

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.

Subgroup Analyses

Prespecified subgroup analyses were performed across demographic (Figure 2) and baseline characteristics (Figure 3). 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 patients. It is worth noting that the ApoE ε4 homozygous subgroup is one of the smallest prespecified subgroups with 132 and 136 patients 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.[9,10]

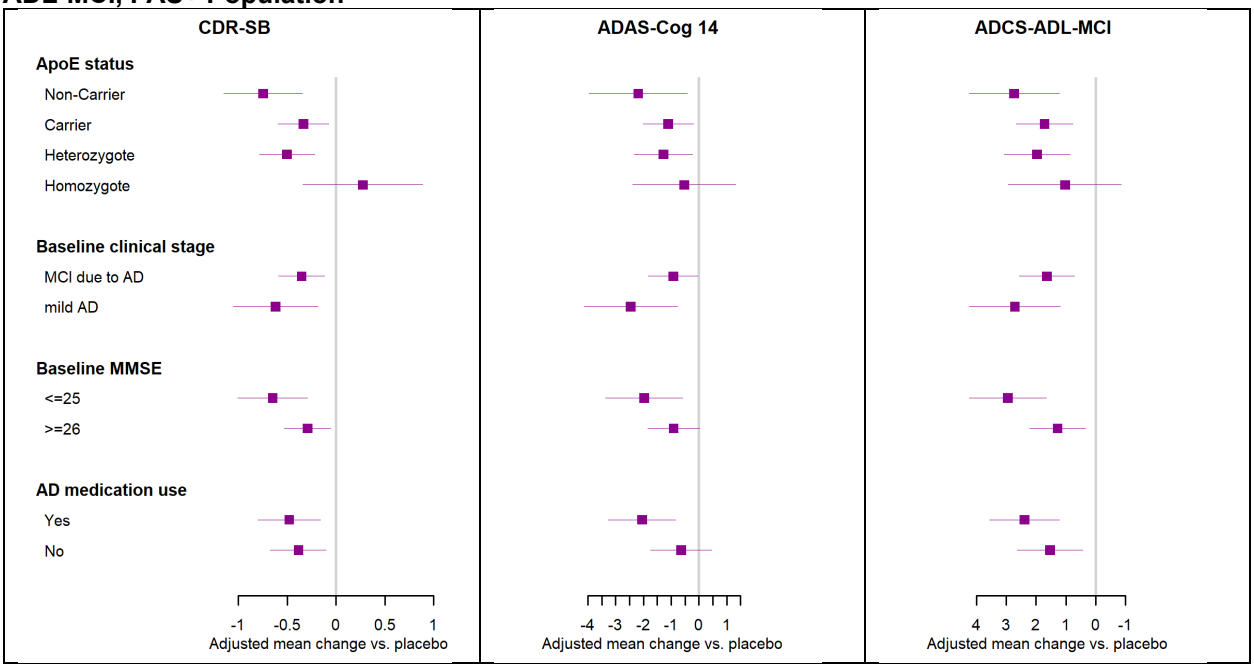
Figure 2. Subgroup Analyses (Demographics) for CDR-SB, ADAS-Cog 14, and ADCS-ADL-MCI, FAS+ Population



Source: Created by the reviewer.
Area to the left of vertical axis signifies treatment effect favoring lecanemab
Abbreviations: ADAS-Cog 14, 14-item Alzheimer's Disease Assessment Scale - Cognitive Subscale; ADCS-ADL-MCI, Alzheimer's Disease Cooperative Study - Activities of Daily Living Scale for use in Mild Cognitive Impairment; CDR-SB, Clinical Dementia Rating-Sum of Boxes; FAS+, full analysis set

[9] Shcherbinin S, CD Evans, M Lu, SW Andersen, MJ Pontecorvo, BA Willis, I Gueorguieva, PM Hauck, DA Brooks, MA Minutn, and JR Sims, 2022, Oct 1, Association of Amyloid Reduction After Donanemab Treatment With Tau Pathology and Clinical Outcomes: The TRAILBLAZER-ALZ Randomized Clinical Trial, 79(1):1015-1024.
[10] Food and Drug Administration, Peripheral and Central Nervous System (PCNS) Drugs Advisory Committee Meeting: Combined FDA and Applicant PCNS Drugs Advisory Committee Briefing Document (Nov. 6, 2020)

Figure 3. Subgroup Analyses (Disease Characteristics) for CDR-SB, ADAS-Cog 14, and ADCS-ADL-MCI, FAS+ Population



Source: Created by the reviewer.
Area to the left of the vertical axis signifies treatment effect favoring lecanemab.
Abbreviations: ADAS-Cog 14, 14-item Alzheimer's Disease Assessment Scale - Cognitive Subscale; ADCS-ADL-MCI, Alzheimer's Disease Cooperative Study - Activities of Daily Living Scale for use in Mild Cognitive Impairment; CDR-SB, Clinical Dementia Rating-Sum of Boxes; FAS+, full analysis set

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 (Table 4). No treatment effect was observed for the EQ-5D-5L by care partner or by care partner as proxy.

Table 4: Health-Related Quality of Life Assessment Analysis, Week 79, FAS+ Population, Study 301

Health-Related Quality of Life Assessment	Placebo Decline (N=875)		Lecanemab (N=859)		
	n	Adjusted Mean	n	Difference vs. Placebo (%)	(95% CI)
EQ-5D-5L (subject): Health Today	754	-4.1	716	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 in Study 301 CSR
Abbreviations: EQ-5D-5L, European Quality of Life-5 Dimensions 5-Level version ; QOL-AD, Quality of Life in Alzheimer's Disease; FAS+, full analysis set

Biomarker Endpoints

Amyloid PET

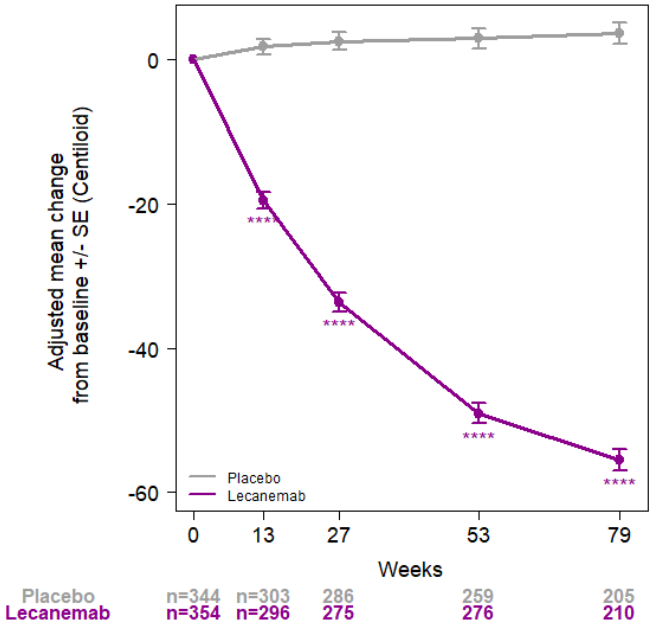
Amyloid PET was assessed in 40% of the overall population (353 patients in the placebo arm and 363 patients in the lecanemab treatment arm). Lecanemab treatment demonstrated a statistically significant treatment effect on change from baseline in brain amyloid as measured by PET and reported as Centiloids at Week 79 (-59.1, p<0.00001) (Table 5). The results indicate a time-dependent relationship (Figure 4). The median [25^{th} – 75^{th} percentile] Centiloid value in lecanemab treated patients at Week 79 was 16.5 [3.8 – 37.3].

Table 5. 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

Figure 4. Change From Baseline in Brain Amyloid (Centiloid), Study 301



Source: Tables 14.2.2.1.1 and 14.2.2.1.2 in Study 301 CSR
*p<0.05, **p<0.01, ***p<0.001, ****p<0.0001
Abbreviations: SE, standard error

Tau PET

Tau PET was evaluated in 257 patients (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 (Table 6). 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 6. Summary of Tau PET Regional Analysis, Week 79

	Baseline SUVR		LS Mean Change From Baseline		
Region	Lecanemab (N=135)	Placebo (N=122)	Lecanemab (N=135)	Placebo (N=122)	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 14.2.7.2.2 in Study 301 CSR
Abbreviations: CI, confidence interval; LS, least squares; PET, positron emission tomography; SUVR, standardized uptake value ratio

vMRI

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 patients to further understand the clinical implications, if any, of these observations.

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 is therefore 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 7. Summary of vMRI Analysis, Week 79

	Baseline (m^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	3245	-95	-106	11 (4, 19)
Right hippocampal	3364	3385	-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)

Source: Tables 14.2.7.5.1 and 14.2.7.5.2 in Study 301 CSR
* Cortical thickness is measured in mm
Abbreviations: CI, confidence interval; LS, least squares; vMRI, volumetric magnetic resonance imaging

Fluid 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.

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

3.1.4 Efficacy Summary

The Applicant has submitted the results of Study 301 as the primary evidence of effectiveness. Study 301 was a large, multicenter trial that demonstrated lecanemab, as compared to placebo, reduced the change from baseline on the primary endpoint, CDR-SB (-0.451, p=0.00005). The Division considers the CDR-SB 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 considered to

be clinically meaningful for an individual patient. Therefore, any 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 is considered clinically meaningful.

The finding on the primary endpoint is supported by statistically significant results for all 4 multiplicity-controlled secondary endpoints, including clinical endpoints capturing distinct information regarding cognitive decline. Statistically significant effects on ADAS-Cog 14 (-1.442. p=0.00065) and ADCS-ADL-MCI (2.016, p<0.00001), endpoints which are independent assessments of cognition and daily function, represent another acceptable co-primary endpoint approach in studies of AD. These results provide further support for the clinical meaningfulness for the changes observed on the CDR-SB. Statistically significant treatment effects were maintained in sensitivity analyses and similar results were obtained with the FAS+ and FDA FAS analysis sets.

The treatment effect in Study 301 is supported by the consistently favorable results for the primary and secondary endpoints across the prespecified subgroups of interest defined by demographic and baseline disease characteristics. Brain Aβ measured by PET was significantly reduced in a time-dependent manner. Biomarkers reflecting target engagement (brain Aβ reduction), effects on downstream tau pathophysiology (tau PET), and neurodegeneration (t-tau) support the observations on the clinical outcome measures.

3.2 Safety Issues

As outlined below, and as previously identified in the original accelerated approval of lecanemab, the main safety signals associated with the use of lecanemab are amyloid related imaging abnormalities (ARIA), cerebral hemorrhage, and infusion-related reactions and hypersensitivity.

Monoclonal antibodies directed against aggregated forms of beta amyloid, including lecanemab, can cause ARIA, classified 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. Microhemorrhage and superficial siderosis, as well as mild focal edema, can occur spontaneously in patients with Alzheimer's disease in the absence of treatment with amyloid targeting therapies and may be related to underlying amyloid burden or CAA; these are usually observed as incidental findings on MRI. In the setting of treatment with monoclonal antibodies directed against aggregated forms of beta amyloid, ARIA-H generally occurs in association with an occurrence of ARIA-E. ARIA-H of any cause (sporadic or drug-related) and ARIA-E can occur together. ARIA 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 label for lecanemab currently describes ARIA and provides monitoring and dose management guideline in the Warnings and Precautions Section 5.1 and in Section 2.3.

The presence of the ApoE ε4 allele increases the risk of ARIA, with greater risk observed in homozygotes than heterozygotes. The use of antithrombotic medication, particularly, anticoagulation therapy, may increase the risk for cerebral hemorrhage in patients taking lecanemab. These risks do not appear to preclude traditional approval. Risk can be mitigated through a description in labeling and recommendations for monitoring and dose management guidelines as provided for in labeling.

An unanswered question is whether the risk of serious outcomes from ARIA are increased in subjects with underlying CAA, noting that there is a substantial overlap between individuals who carry the ApoE ε4 allele and have CAA pathology and that ApoE ε4 homozygotes have been found to have a greater severity of CAA pathology at autopsy. 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 this disorder difficult and limits the ability 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 potential for these risks needs to be considered in the benefit-risk discussion between prescribers and patients/caregivers when making the decision to initiate therapy.

3.2.1 Sources of Data for Safety

The primary source of data for assessment of safety in the present submission is the randomized, placebo-controlled Study 301 Core that is the confirmatory study and its open label extension, 301 OLE, in subjects with mild cognitive impairment or mild dementia due to AD. In Study 301, lecanemab was given at a dose of 10mg/kg biweekly, the currently approved dose; that dose will be referred to as lecanemab.

3.2.2 Safety Summary

Across the development program, 2345 subjects have been exposed to at least one dose of lecanemab at any dose, including 898 in 301 Core and 714 in 301 OLE (1612 total in 301 Core and OLE) exposed at a dose of 10 mg/kg. 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. These numbers exceed the ICH guidelines of 300 subjects for 6 months, and 100 subjects for 1 year. Across the development program, 1604 subjects were exposed to lecanemab 10 mg/kg biweekly for at least 6 months, 1261 for at least 12 months, and 965 for at least 18 months. The safety database is adequate to assess the safety of lecanemab 10 mg/kg biweekly.

Deaths and Serious Adverse Events

Overall, in 301 Core and OLE the incidence of death was 6.9/1000 person years (16/2331.2 person years). In 301 Core, there was no imbalance in deaths for which the precipitating event occurred within 30 days of a dose for lecanemab (0.7%, 6/898) compared to placebo (0.8%, 7/897). 1 additional death each in lecanemab (diabetic ketoacidosis) and placebo (cardiorespiratory arrest) occurred more than 30 days after the last dose. In 301 Core, a role for lecanemab in the deaths is not apparent, there is no unusual cluster of deaths, and none was preceded by ARIA. Serious adverse events (SAEs) occurred more frequently in the lecanemab group and were driven by infusion-related reactions and ARIA-E. SAEs

occurring in at least 5 subjects and more frequently than in placebo in 301 Core are shown in Table 8 below.

Table 8. Most Common Treatment Emergent SAEs, Study 301 Core

SAEs	Lecanemab N=898 n (%)	Placebo N=897 n (%)
SAEs (total)	126 (14)	101 (11)
Infusion-related reactions	11 (1.2)	0
ARIA-E	7 (0.8)	0
Syncope	6 (0.7)	2 (0.2)
Atrial fibrillation	6 (0.7)	3 (0.3)
Angina	6 (0.7)	0

Source: adae.xpt (created by clinical analyst)
Abbreviations: ARIA-E, amyloid related imaging abnormalities with edema; SAE, serious adverse event

The incidence of SAEs in 301 OLE was 9% (126/1385) and was driven by ARIA-E (0.8%) and infusion related reactions (0.7%).

In 301 OLE the incidence of deaths was 0.7% (9/1385). A role for lecanemab in 6 of the 9 deaths is not apparent.

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

- Intracerebral hemorrhage was reported in an 88 year-old male, ApoE ε4 noncarrier, with past medical history including atrial fibrillation, hyperlipidemia, coronary artery disease, and lacunar stroke, with 3 microhemorrhages at baseline, and baseline medications including baby aspirin and the anticoagulant apixaban. The subject was randomized to placebo in 301 Core. In the OLE, the subject had a fall on Day 77 after 6 doses of lecanemab, followed by COVID-19 on Day 98 (with "protease inhibitors 150/100 mg/mg PO QD" for 5 days). This was complicated by 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 left occipital cerebral hemorrhage greater than 1 cm, ARIA-E in the left occipital area, and a new ARIA-H microhemorrhage in the left frontal area. Apixaban 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 TIA-like events on Day 128 and was started on clopidogrel. The subject enrolled in hospice and was treated with clopidogrel and lorazepam and died on Day 144. Brain autopsy did not show gross evidence of amyloid angiopathy; 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, that 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. The role of ARIA-H, ARIA-E, and cerebral hemorrhage in the death is unclear, given the concurrent medical events.
- Acute multifocal intracerebral hemorrhage was reported in a 65 year-old female, homozygous for ApoE ε4, with no microhemorrhages or superficial siderosis at screening MRI. Her relevant past medical history was patent foramen ovale. The subject completed 301 Core on placebo. Based on

the adverse event dataset, she started complaining about headaches after the first dose of lecanemab in the open-label extension phase. Four days after the 3rd dose of lecanemab, she experienced garbled speech and left gaze preference. A CT scan showed hypodensities in the left temporal, and parietal and right occipital region, and an occlusion of the M3 branch of the left middle cerebral artery. An occlusive left sided ischemic stroke due to an LM3 occlusion was diagnosed. 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 nonconvulsive seizures. 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 an acute right thalamocapsular infarct and innumerable multifocal cortical intracerebral hemorrhages with edema with innumerable hematomas, subarachnoid hemorrhage, and right intraventricular hemorrhage. The subject was extubated and died 8 days after the dose of lecanemab. Subsequent autopsy reported cause of death as nontraumatic intracerebral hemorrhage and showed extensive, multi-focal intraparenchymal hemorrhage, cerebral amyloid angiopathy, high Alzheimer's disease neuropathologic changes and diffuse histiocytic vasculitis with necrotizing vasculopathy involving amyloid deposition within (but not outside) the blood vessel walls. Although 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.[11,12,13,14] 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, a role of lecanemab cannot be ruled out. 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 diffuse histiocytic vasculitis is not known.

- Possible seizure and possible cerebrovascular accident were reported in a 79 year-old female, ApoE ε4 homozygote, with underlying CAA who had been randomized to placebo in 301 Core. The details of this case have been reported in a pre-print manuscript[15] that has not been peer-reviewed, and for which Eisai has not been able to obtain critical documents substantiating the findings. Therefore,

[11] 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]

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the following should be interpreted with caution, with the recognition that firm conclusions cannot be made regarding the events. According to the narrative provided by Eisai, 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 but not confirmed by Eisai, the pre-treatment MRI before the open label extension showed 4 small cerebral microhemorrhages. 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 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 evaluated for acute stroke but felt to not be a good candidate for tPA. According to the manuscript, MRI showed multifocal cerebral edema more than 30 microhemorrhages. The neuroimaging findings were consistent with ARIA. She 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 expired 5 days after hospital admission. The Agency has not received the official autopsy report or MRI images from the hospitalization. The autopsy results of this participant reported in the manuscript describes severe amyloid angiopathy with features suggestive of CAA-related inflammation/vasculitis, similar to the autopsy findings of the participant 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 patients with pathologically confirmed Alzheimer's disease found that approximately 73% of ApoE ε4 homozygotes in the study population had severe CAA compared to approximately 27% that had no CAA, and patients with CAA were more likely to have intracerebral hemorrhage than patients without CAA (9.3% vs 3.5%).[16]

There were 2 deaths in the setting of cerebral hemorrhage that occurred in ApoE 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 subjects with Alzheimer's disease, as noted above, but there is a lack of definitive clinical criteria for diagnosing CAA. This results in inability to compare the risk of cerebral hemorrhage in lecanemab-treated subjects with or without CAA and leads to substantial uncertainty and limits the ability to make any recommendations regarding the use of lecanemab in subjects with CAA. Of note, postmarketing pharmacovigilance for vasculitis was requested upon the accelerated approval of lecanemab.

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Discontinuations

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, 4.1% (57/1385) of subjects discontinued lecanemab due to adverse events. The most common reasons for study drug discontinuations during the 301 OLE were similar to the 301 Core phase and included ARIA-E (1.2%), ARIA-H (0.8%), and infusion-related reactions (0.8%).

Treatment Emergent Adverse Events

The incidence of treatment-emergent adverse events (TEAEs) in 301 Core was 89% in the lecanemab arm and 82% in the placebo arm. A summary of TEAEs in 301 Core is shown in Table 9. The most frequently reported TEAEs in 301 on lecanemab were infusion related reaction, ARIA-H, ARIA-E, and headache. Of note, these TEAEs do not include individual TEAEs associated with events of ARIA.

Table 9. Adverse Reactions Reported in at Least 5% of Subjects Treated With Lecanemab and at Least 2% Higher Than Placebo, Study 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)	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[2]	37 (4)	52 (6)
Nausea and vomiting	37 (4)	50 (6)

Source: adae.xpt (created by clinical analyst)
[a] 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

In Study 301 OLE Phase, the most common (>10%) TEAEs were similar to 301 Core: infusion related reaction (13%), COVID-19 (13%), and ARIA-H microhemorrhages (12%).

Adverse Events of Special Interest

Amyloid-Relating Imaging Abnormalities (ARIA)

Incidence

Monoclonal antibodies directed against aggregated forms of beta amyloid, including lecanemab, can cause amyloid related imaging abnormalities (ARIA). Table 10 shows the incidence of ARIA events, within 30 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.

Table 10. Incidence of Treatment Emergent ARIA Events, Study 301 Core

ARIA Events	Lecanemab N=898 n (%)	Placebo N=897 n (%)
ARIA	191 (21)	84 (9)
ARIA-E	113 (13)	15 (2)
ARIA-H*	152 (17)	80 (9)
Superficial siderosis	50 (6)	21 (2)
ARIA-microhemorrhage	126 (14)	68 (8)

Source: adae.xpt (created by clinical analyst)
* exclusive of cerebral hemorrhage
Abbreviations: ARIA, amyloid related imaging abnormalities; ARIA-E, ARIA with edema; ARIA-H, ARIA with hemosiderin deposition

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 mostly driven by an increase in the incidence of ARIA-H in 301 Core, which occurred in 6% on lecanemab and 5% on placebo in 201 Core. 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 patients who did not have ARIA-H at the same time on any given MRI) was 4% (36/898) on lecanemab, versus 0.4% (4/897) on placebo. There was little imbalance in isolated ARIA-H between lecanemab (9%, 78/898) and placebo (8%, 69/897) in 301 Core, consistent with the observation in 201 Core. Among new lecanemab exposures in 301 OLE (n=714), the incidence of ARIA (20%), ARIA E (14%), and ARIA-H (15%) were also 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 similar to that in 301 Core alone.

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. 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 participants 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.

In 301 Core approximately 25% (28/113) of subjects with ARIA-E on lecanemab had more than 1 treatment-emergent event of ARIA E; 4 of those subjects had more than 2 events. This included subjects in whom lecanemab was interrupted because of ARIA and then resumed. Among subjects with more than 1 event, 71% were ApoE ε4 homozygotes and 25% were heterozygotes. 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.

ApoE ε4 Genotype

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. In 301 Core, 16% (141/898) of subjects in the LEC10-BW 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 Table 11, below. Similar findings were observed in subjects who were new to lecanemab in 301 OLE.

Table 11. Incidence ARIA ApoE Genotype in Subjects Exposed to Lecanemab, Study 301 Core

	Noncarriers	**Heterozygotes**	**Homozygotes**
	N=278	N=479	N=141
	N (%)	N (%)	N (%)
ARIA	38 (14)	92 (19)	63 (45)
ARIA-E	15 (5)	52 (11)	46 (33)
ARIA-H**	32 (12)	66 (14)	54 (38)

Source: adae.xpt (created by clinical analyst)
**ARIA-H includes microhemorrhages and superficial siderosis, does not include *cerebral hemorrhage*
Abbreviations: ApoE, apolipoprotein E; ARIA, amyloid related imaging abnormalities; ARIA-E, ARIA with edema; ARIA-H, ARIA with hemosiderin deposition

Among the 9 subjects with treatment emergent cerebral 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. The limited data do not allow for a conclusion about the risk of cerebral hemorrhage in ApoE ε4 carriers.

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% were ApoE ε4 homozygotes, 41.3% were heterozygotes, and 14% were noncarriers. The most common symptom in subjects with ARIA on lecanemab was headache; 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 92% (23/25) of subjects with symptomatic ARIA-E and 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.

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, subjects with Alzheimer's disease may be at increased risk for seizures.[17] 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 1%, 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

Routine Safety MRIs to monitor for ARIA were to be performed to prior to the 5th, 7th, 14th, 28th, and 40th doses and 2 weeks after the last dose in 301 Core.

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. Additional ARIA-E events continued to occur up to the 39th dose. Of subjects with ARIA-E, approximately 8% 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 14th dose.

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.

Antithrombotic Use

In Study 301, anticoagulation was to be allowed if anticoagulation was optimized and stable for at least 4 weeks before screening. If treatment with thrombolytic drugs was required, study drug was to be temporarily suspended until stabilization or resolution of the medical condition requiring thrombolytic therapy. The protocol also excluded subjects 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 subjects 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.

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

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 have an antithrombotic medication preceding ARIA-H. In subjects treated with lecanemab in 301 Core, subjects who received antithrombotic medication preceding a cerebral hemorrhage event had a slightly higher incidence of cerebral hemorrhage (0.9%, 3/328), 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), although the small number of events limits definitive conclusions. The limited number of cerebral hemorrhage events on subjects taking placebo preclude a comparison with the risk of antithrombotic use in placebo. A similarly increased risk of cerebral 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 (75%, 468/625). 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 subject already being treated with lecanemab.

Seizures

In Study 301 Core the incidence of having a seizure was 0.7% (6/898) of patients on lecanemab and 0.4% (4/897). One participant 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. Two patients (1 in 301 Core and 1 in 301 OLE, included above) had seizures in the setting of cerebral hemorrhage.

Infusion-related Reactions and Hypersensitivity

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 was mild in 69% of lecanemab subjects, moderate in 28% and severe in 3%. Eleven subjects (1.2%) 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 6/897 (0.7%) 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.

Ninety-four percent (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 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 one subject with blood pressure of 180/85 mm Hg approximately 4 hours after an infusion and one subject 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 commonly described in Core 201 that included fever and flu-like symptoms (chills, generalized aches, feeling shaky, and joint pain). Some participants experienced hypotension, hypertension, nausea, vomiting, or desaturation.

One subject 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.

Safety Conclusion

In summary, the main safety signals associated with the use of lecanemab are ARIA, cerebral hemorrhage, and infusion-related reactions and hypersensitivity. The presence of ApoE ε4 increases the risk of ARIA in a dose-dependent manner. The use of antithrombotic therapy, and anticoagulant therapy in particular, may increase the risk for cerebral hemorrhage in subjects taking lecanemab. The safety findings observed in the confirmatory Study 301 Core are consistent with the findings observed in the original review of lecanemab and consistent with findings associated with the class of monoclonal antibodies directed against aggregated forms of beta amyloid.

Two deaths occurred in subjects who had cerebral hemorrhage after treatment with lecanemab and 1 death occurred in a patient with a possible cerebrovascular accident and severe ARIA-E and ARIA-H. Uncertainty regarding the role of lecanemab in these cases includes the role of concomitant medications, possible contribution of ARIA, the possible presence of cerebral amyloid angiopathy and related vasculitis and its role in such events.

The adverse events associated with infusion reactions in the confirmatory study are generally similar to those previously identified in 201 Core. Newly identified signals include a case of anaphylaxis

The risks can be described in the prescribing information and do not appear to preclude traditional approval of lecanemab.

3.3 Risk Mitigation

The risks of ARIA and cerebral hemorrhage and the risk of infusion-related reactions are described as Warnings and Precautions in the currently approved labeling,

MRI monitoring at intervals recommended in the currently approved label appear to be appropriate for identification of most ARIA. In the clinical trials, additional MRI evaluation was performed in response to

symptoms. Consideration should be given as to whether specific adverse events, such as headache, in patients at increased risk for ARIA such as ApoE ε4 homozygotes, should explicitly elicit additional monitoring.

As noted above, although 2 deaths in the setting of cerebral hemorrhage occurred in ApoE ε4 homozygous subjects with underlying severe CAA, any role for an interaction between lecanemab and underlying severe CAA or CAA-related inflammation/vasculitis cannot be determined. The two fatalities occurred in the OLE with no comparator control group. There is a high background prevalence of CAA in subjects with Alzheimer's disease, and a lack of definitive criteria for diagnosing CAA. This results in inability to compare the risk of cerebral hemorrhage in lecanemab-treated subjects with or without CAA and leads to substantial uncertainty in the ability to make any recommendations regarding use of lecanemab in subjects with CAA.

The accelerated approval included a request for expedited reporting of any deaths in ongoing studies and of deaths resulting from cerebral hemorrhage greater than 1 centimeter in size in the postmarketing setting. It also requested postmarketing pharmacovigilance to characterize the risk of ARIA and the monitoring for ARIA associated with the use of lecanemab, including evaluation of central nervous system hemorrhage in patient with pre-existing risk factors for bleeding, including concomitant medications that could increase the risk for bleeding. The accelerated approval also included a request for identification and analysis of vasculitis after use of lecanemab. If lecanemab receives traditional approval, these aspects of postmarketing pharmacovigilance will continue.

The approved labeling for Leqembi calls attention to the Alzheimer's Network for Treatment and Diagnostics (ALZ-NET), a voluntary provider-enrolled patient registry that collects information on treatments for Alzheimer's disease, including Leqembi. It is expected that the ALZ-NET registry will contribute to a more complete understanding of the risks and opportunities to minimize the risks of this class of drugs in general and of lecanemab in particular.

4 References

See footnotes throughout the document.