CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761269Orig1s000

SUMMARY REVIEW

Summary Memorandum

Date	January 5, 2022
From	Ranjit Mani, MD Cross-Discipline Team Lead, Division of Neurology 1 (DN1) Sally Jo Yasuda, PharmD Deputy Director for Safety, DN1 Teresa Buracchio, MD Director, DN1 Billy Dunn, MD Director, Office of Neuroscience
Subject	Summary Memorandum
BLA #	761269
Applicant	Eisai Inc
Date of Submission	December 14, 2021
PDUFA Goal Date	January 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	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 6.2 million Americans age 65 and older are currently living with AD dementia, and AD is the sixth 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 is an anti-amyloid beta-directed antibody approved under that 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. This approval was 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 drugs that target the underlying pathophysiology of AD in an effort to fundamentally affect the course of the disease an important focus of development.

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 accelerated approval based on reduction in amyloid plaque burden measured by positron emission tomography (PET) imaging which is proposed to be reasonably likely to predict clinical benefit. This submission contains biomarker, efficacy, and safety data from Study 201, 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. The study included a 2-month screening period, an 18-month (78-week) placebo-controlled treatment period, and a safety follow-up period of 3

months after the final dose. For the placebo-controlled period, patients were randomized to placebo or one of 5 lecanemab dosing regimens, including the intended dosing regimen of 10 mg/kg biweekly. The primary clinical endpoint was the change from baseline in a cognitive composite measure, Alzheimer's Disease Composite Score (ADCOMS), at Week 53. Change from baseline in brain amyloid plaque as measured by 18F-florbetapir PET and quantified by a composite standard uptake value ratio (SUVR) was assessed in a subset of patients at Week 53 and Week 79 and serves as the endpoint to support accelerated approval.

Lecanemab reduced brain amyloid plaque in a dose- and time-dependent manner. The lecanemab 10 mg/kg biweekly arm had a statistically significant reduction in brain amyloid plaque from baseline to Week 79 compared to the placebo arm (mean difference of -0.31 SUVR or -73.5 Centiloids; $p<0.001$). The primary analysis of ADCOMS at Week 53 indicated that the lecanemab 10 mg/kg biweekly dosing regimen had a 64% probability of being superior to placebo by 25%. Prespecified analyses of data at Week 79 suggested reduced decline on clinical endpoints by approximately 20% to 40%.

The Agency has previously found with the accelerated approval of aducanumab that reduction of brain Aβ plaque on PET is reasonably likely to predict clinical benefit in Alzheimer's disease. This determination was based on the character of brain Aβ plaque as an underlying, fundamental, and defining pathophysiological feature of the disease, and modeling that demonstrated a clear exposure-response relationship between reduction of brain Aβ plaque and preservation of clinical function that was consistent across aducanumab and all 6 other available programs of anti-amyloid beta antibodies under development over the past decade, based on a review of publicly available information.

Accelerated approval is intended for serious conditions where the drug provides a meaningful advantage over available therapies. Accelerated approval is based on an outcome that is reasonably likely to predict clinical benefit, rather than on the clinical benefit itself. These outcomes predictive of benefit are generally surrogate markers of disease of some sort, but may also be an intermediate clinical endpoint that can be measured earlier than the outcome of ultimate clinical importance. Substantial evidence of effectiveness is required on such an endpoint to support accelerated approval, just as it is required for an endpoint supporting standard approval.

With regard to the evidence of effectiveness supporting accelerated approval on the basis of a reduction in amyloid beta plaque, the requirements are met. Study 201 was an adequate and well-controlled study that demonstrated clear and persuasive highly statistically significant dose- and time-dependent reductions of Aβ plaque on PET imaging, a surrogate endpoint that has been determined to be reasonably likely to predict clinical benefit. These findings are supported by a reduction in decline on clinical outcome measures in the study. Although not yet submitted to the Agency for review, it is also notable that the topline results of Study 301, a randomized, double-blind, placebo-controlled Phase 3 study in Alzheimer's

disease, have been publicly reported and appear to support the clinical benefit of Aβ plaque reduction. Given the robust, persuasive, and consistent effects of lecanemab on an acceptable surrogate endpoint, brain Aβ plaque on PET, Study 201 can be considered a single adequate and well-controlled trial that provides substantial evidence of effectiveness.

Alzheimer's disease is a serious and life-threatening condition with a tremendous unmet medical need. This unmet need is not only well recognized by the Agency and the scientific community, but is clearly articulated by the voices of Alzheimer's disease patients and their caregivers who leave no doubt of the urgent need for an effective treatment. This is exactly the situation for which accelerated approval exists – where the evidentiary criteria for accelerated approval are met, it can provide earlier access to a promising drug to patients with unmet needs. There is substantial evidence that lecanemab reduces Aβ plaques, and this reduction is reasonably likely to result in clinical benefit for patients.

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 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.

The safety of lecanemab was characterized in a safety database with 1 year exposure meeting the ICH E1 guideline for long-term treatment of non-life-threatening conditions. Although the 6- month exposure numbers did not meet the ICH E1 guideline, the Division considers that the number of 1 year exposures and the determination that Alzheimer's disease is a serious and life-threatening disease offset those limitations.

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 was observed in 12% of participants treated with lecanemab 10 mg/kg biweekly (20 out of 161) compared to 5% participants on placebo (13 out of 245).

In the lecanemab 10 mg/kg biweekly arm, ARIA-E was observed in 10% of treated participants compared to 1% of participants

on placebo. Symptomatic ARIA occurred in 3% (5 out of 161) of participants treated with lecanemab 10 mg/kg biweekly in Study 201 and in none of the participants on placebo. The most common symptoms in participants treated with lecanemab 10 mg/kg biweekly, that occurred in 2 or more participants who had an observation of ARIA, were headache, confusion/mental status changes, agitation and visual disturbance. Clinical symptoms resolved in 4 out of 5 participants during the period of observation.

The incidence of ARIA-E was higher in apolipoprotein E ε4 (ApoE ε4) homozygotes (5 out of 10) than in heterozygotes (2 out of 39) or in non-carriers (9 out of 112). There were 4 ApoE ε4 homozygotes who had symptomatic ARIA, of whom 2 had severe symptoms. Due to protocol changes to reduce risk in the proposed dose arm during the conduct of Study 201, only 30 % of participants treated with lecanemab 10 mg/kg biweekly were ApoE ε4 carriers compared to up to 60-70 % of individuals with AD in the general population. Therefore, interpretation of ARIA related analyses should consider the limitations of the small number of ApoE ε4 carriers in the proposed dose. However, published topline results from Study 301 also suggest a higher incidence of ARIA overall and symptomatic ARIA in ApoE ε4 homozygotes compared to heterozygotes and noncarriers; those results have not yet been verified by the Agency.

The majority of ARIA-E radiographic events occurred within the first three months during treatment, although ARIA can occur at any time. Of the 16 participants treated with lecanemab 10 mg/kg biweekly who had ARIA-E, the maximum radiographic severity was mild in 7, moderate in 7, and severe in 2. In the lecanemab 10 mg/kg biweekly arm, resolution occurred in 62 % of ARIA-E participants by 12 weeks, 81% by 21 weeks, and 94% overall after detection. There was no imbalance in isolated ARIA-H between lecanemab and placebo. Cerebral hemorrhage greater than 1 cm was reported in 1 participant on lecanemab 10 mg/kg biweekly and in no participants on placebo in Study 201. Events of intracerebral hemorrhage greater than 1 cm in diameter in patients taking lecanemab 10 mg/kg biweekly have also been reported in Study 301 and its extension study. There were no deaths due to ARIA in Study 201. Patients who received lecanemab and an antithrombotic medication (aspirin, other antiplatelets, or anticoagulants) did not have an increased risk of ARIA-H compared to patients who received placebo and an antithrombotic medication. In the placebo-controlled period of Study 201, lecanemab was to be discontinued if ARIA occurred. Limited data are available from the open label extension phase of Study 201 on the safety of continued dosing after ARIA-E with lecanemab.

Infusion-related reactions occurred in 20% of patients on lecanemab 10 mg/kg biweekly versus 3% in placebo. Infusion reactions were mild (56%) or moderate (44%) in severity, and 88% occurred at the time of the first infusion. Symptoms included fever and flu-like symptoms (chills, generalized aches, feeling shaky and joint pain).

The most common adverse drug reactions with lecanemab are ARIA-E, infusion related reactions, and headache. All occurred in

at least 10% of participants on the proposed dose of lecanemab 10 mg/kg biweekly and at least 2% more frequently than placebo in the controlled period of Study 201.

In summary, substantial evidence of effectiveness has been established on the basis of a reduction in amyloid beta plaque which supports accelerated approval of lecanemab for the treatment of Alzheimer's disease. The applicant proposes to submit data from Study 301 as soon as possible to fulfill the requirement to confirm the benefit the clinical benefit of lecanemab for the treatment of Alzheimer's disease. 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. ARIA will receive a warning in labeling describing the risk along with monitoring and dosing recommendations. The applicant will provide a structured educational program for clinicians involved with lecanemab treatment, and will be identifying and characterizing cases of ARIA when used clinically. It is possible that the character of ARIA will be different in clinical practice than in clinical studies. 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.

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 6.2 million Americans age 65 and older are currently living with Alzheimer's disease. • Alzheimer's disease is the sixth 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 is an anti-amyloid beta-directed antibody approved under that 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. This approval was based on a demonstration reduction of amyloid beta on PET imaging, a surrogate endpoint that was determined to be reasonably likely to predict clinical	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
	benefit. • 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 201
	  • Participants were randomized to receive placebo or a range of lecanemab dosing regimens.
	  • The trial enrolled 856 patients: 609 in lecanemab treatment arms and 247 in the placebo arm.
	  • The primary endpoint was the change from baseline in ADCOMS. The ADCOMS is a weighted linear combination of items from 3 commonly used scales: ADAS-Cog, MMSE, and CDR-SB. ADAS-Cog and CDR-SB were key secondary endpoints.
	  • Change from baseline in brain amyloid plaque as measured by 18F-florbetapir PET and quantified by a composite SUVR was assessed in a subset of patients and listed as a key secondary endpoint in the protocol.
	• Lecanemab reduced brain amyloid plaque in a dose- and time-dependent manner. Brain amyloid plaque showed a reduction from 1.37 SUVR (78.0 Centiloids) at baseline to 1.07 SUVR (5.5 Centiloids) at Week 79 in the 10 mg/kg biweekly arm, compared to a value of 1.40 SUVR (84.8 Centiloids) at baseline and 1.40 SUVR (85.8 Centiloids) at Week 79 in the placebo arm. The lecanemab 10 mg/kg biweekly arm had a statistically significant reduction in brain amyloid plaque from baseline to Week 79 compared to the placebo arm (mean difference of -0.31 SUVR or -73.5 Centiloids; $p<0.001$).
	• The primary Bayesian analysis of ADCOMS at Week 53 indicated that the lecanemab 10 mg/kg biweekly dosing regimen had a 64% probability of being superior to placebo by 25%.
	• The 10 mg/kg lecanemab treatment regimen demonstrated favorable numerical results for ADCOMS and CDR-SB and nominal statistical significance for ADAS-Cog 14 at Week 79.
		The applicant has demonstrated a robust and statistically significant treatment-related reduction in brain amyloid plaque in patients at the early stages of symptomatic Alzheimer's disease. The decrease in brain amyloid plaque demonstrated for lecanemab is consistent with the reduction established for aducanumab, a drug that received accelerated approval based on a conclusion that the decrease in brain amyloid plaque was reasonably likely to predict clinical benefit. The observed effects of lecanemab on clinical endpoints in Study 201 contributed to the reasonable likelihood that a lowering of amyloid beta plaque will result in clinical benefit.
		
		A requirement to conduct a clinical trial to confirm the benefits of lecanemab in AD will be issued as a post-marketing requirement (PMR). The applicant proposes to submit data from the recently completed Study 301 as soon as possible to fulfill the requirement to confirm the benefit the clinical benefit of lecanemab for the treatment of Alzheimer's disease.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk and Risk Management	• The safety database includes 763 participants exposed to at least one dose of lecanemab. This includes 237 participants 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 and 217 for at least 12 months without interruption (as there was a gap ranging from 9-56 months between exposure in the 201 Core (double blind placebo-controlled period) and OLE (open label extension phase). • The most common TEAEs in Study 201 Core (at least 5% and at least 2% greater than placebo) were infusion-related reactions (20%), ARIA-E (10%), headache (14%), cough (9%), and diarrhea (8%). • ARIA was observed in 12 % (20/161) of participants treated with lecanemab 10 mg/kg biweekly, compared to 5 % (13/245) of participants on placebo in Study 201 Core. • Symptomatic ARIA occurred in 3% (5/161) of patients treated with lecanemab compared to 0/245 on placebo in Study 201 Core. Of these 5 patients, 4 were ApoE ε4 homozygotes, of whom 2 experienced severe symptoms. The clinical symptoms observed in 2 or more participants treated with lecanemab 10 mg/kg biweekly who had an observation of ARIA were headache, confusion or mental status changes, agitation, and visual disturbances. Other symptoms reported include burning sensation, paresthesia, labile affect, aphasia, confabulation, hallucination, transient ischemic attack, vomiting and possible seizure each of which occurred in 1 participant. • ARIA-E was observed in 10% (16/161) of participants treated with lecanemab 10 mg/kg biweekly compared to 1% (2/245 245) of participants on placebo. Among the 16 participants treated with lecanemab 10 mg/kg biweekly who had ARIA-E, the maximum radiographic severity was mild in 7 participants, moderate in 7 participants, and severe in 2 participants. The majority of ARIA-E	1 year exposures meet the ICH E1 guideline for long-term treatment of non-life-threatening conditions. Although the minimum 6- month exposure numbers of 300 were not met, the Division considers that the number of 1 year exposures and the determination that Alzheimer's disease is a serious and life-threatening disease offset the limitations of the exposure. Risk management for ARIA can be achieved through clear product labeling and monitoring for ARIA, as described in the label. 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. Guidance regarding monitoring and implications regarding a finding of ARIA on subsequent dosing will be provided in Section 2.3 of the prescribing information. MRI prior to the 5th, 7th, and 14th infusions will identify asymptomatic ARIA. Enhanced clinical vigilance is recommended with additional guidance for considerations regarding continued treatment. Because cerebral hemorrhage > 1 cm in diameter may be seen with lecanemab, a statement in the label in Section 5.1 Warnings and Precautions will advise prescribers to exercise additional caution when considering the

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	radiographic events occurred early in treatment (within the first 7 doses). After detection, resolution occurred in 62 % of ARIA-E participants by 12 weeks, 81% by 21 weeks, and 94% overall. The incidence of ARIA-E was higher in ApoE ε4 homozygotes (5/10; 50%) than in heterozygotes (2/39; 5%) or in non-carriers (9/112 (8%). • ARIA-H was observed in 6% of participants on lecanemab 10 mg/kg biweekly compared to 5 % of participants on placebo. There was no imbalance in isolated ARIA-H. One participant had a cerebral hemorrhage greater than 1 cm at the proposed dose arm compared to 0 in placebo. Events of intracerebral hemorrhage greater than 1 cm in diameter in patients taking lecanemab 10 mg/kg biweekly have also been reported in Study 301. • There was no increased risk of ARIA-H in patients who received lecanemab 10 mg/kg biweekly and an antithrombotic medication compared to patients who received placebo and an antithrombotic medication. The incidence of ARIA-H (microhemorrhage and superficial siderosis) in those receiving antithrombotic vs. not in the lecanemab 10 mg/kg biweekly arm was 5/85 (6%) vs. 3/76 (4 %) compared to 6/127 (5%) vs. 5/118 (4%) in the placebo arm in 201 Core. • Infusion-related reactions occurred in 20% of patients on lecanemab 10 mg/kg biweekly vs. 3% in placebo-treated patients. Infusion reactions were mild (56%) or moderate (44%) in severity, and 88% occurred at the time of the first infusion. Symptoms included fever and flu-like symptoms (chills, generalized aches, feeling shaky, and joint pain). Some participants experienced hypotension, hypertension, nausea, vomiting, or desaturation. One participant at the proposed dose arm had an SAE of infusion related reaction. No one had anaphylaxis. Most patients with an infusion reaction (22/27) received premedication prior to subsequent infusions, and 16/22 (72%) did not have a repeat infusion related reaction. Discontinuations due to an infusion reaction were reported in 4/161 (2.5%) patients on lecanemab	administration of antithrombotic or thrombolytic agents (e.g., tissue plasminogen activator) to a patient already being treated with lecanemab, and to consider testing for ApoE ε4 status to inform the risk of developing ARIA. ARIA will also be addressed in the Medication Guide. Prescribers will be made aware of the risk of infusion-related reactions in Section 5.2 of Warnings and Precautions. This will also be addressed in the Medication Guide. Requested postmarketing vigilance will further characterize the uncertainties related to safety of lecanemab.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	10 mg/kg biweekly vs. 1% on placebo. Although not associated with clinically adverse outcomes, there were transient, dose-dependent decreases in lymphocytes and increases in neutrophils and leukocyte counts in lecanemab treated groups compared to placebo that were noted after the first infusion. These changes may be related to an infusion reaction. 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 cerebral 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, 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 participants with lecanemab through episodes of radiographically mild ARIA-E with mild clinical symptoms is unknown. • The safety of treating participants with lecanemab through episodes of radiographically mild, asymptomatic ARIA-H is unknown. • The safety of concomitant use of medications that increase bleeding risk is unknown, as is the risk in patients otherwise at risk for bleeding.	

2. Background

This application under review is for lecanemab (previously BAN2401), 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. It is a new molecular entity (NME) containing no previously approved active ingredient (including any ester or salt of the active ingredient) and is not currently marketed in the United States for any indication.

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 6.2 million Americans age 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 (Alzheimer's Association, 2021).

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 the most recently approved novel medication for AD; it 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 that 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. This approval was 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 drugs that target the underlying pathophysiology of AD in an effort to fundamentally affect the course of the disease an important focus of development efforts.

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 program. 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-hemorrhage (ARIA-H).

In this BLA, the applicant is seeking accelerated approval based on reduction in amyloid plaque burden measured by PET imaging which is proposed to be reasonably likely to predict clinical benefit. This submission contains biomarker, efficacy, and safety data from Study 201, 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. The study demonstrated brain amyloid plaque in a dose- and time-dependent manner. Although not yet submitted to the Agency for review, the applicant has recently completed Study 301, a randomized, double-blind, placebo-controlled Phase 3 study in Alzheimer's disease, and topline results have been publicly reported that appear to support the clinical benefit of Aβ plaque reduction. The applicant proposes to submit this data as soon as possible to fulfill the requirement to confirm the clinical benefit of lecanemab in Alzheimer's disease.

3. Product Quality

The application team lead on the Office of Pharmaceutical Quality (OPQ) review was Dr. Jennifer Swisher. This review lists the entire OPQ team that was involved in that review.

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).

The following conclusion is extracted from the OPQ review:

"The data submitted in this application are adequate to support the conclusion that the manufacture of LEQEMBI is well-controlled and leads to a product that is pure and potent. It is recommended that this product be approved for human use under conditions specified in the package insert."

The basis for that conclusion is explained fully in the OPQ review.

OPQ has identified one product quality-related issue and one immunogenicity assay-related issue, each of which is to be assessed as a post marketing commitments (PMC). These are as follows:

- OPQ recommended a shipping study to confirm validation of the commercial lecanemab drug product shipping conditions. Details of this study are described in the OPQ review

- OPQ also recommended improving the sensitivity for the current anti-drug antibody (ADA) assay to at least 100 ng/mL in the presence of the trough level of drug expected to be present during sampling; and improving the sensitivity and drug tolerance of the current neutralizing antibody (NAb) assay. OPQ further recommended alternative approaches if these improvements could not be made. Further details of the recommended approach to assay validation were provided.

4. Nonclinical Pharmacology/Toxicology

The nonclinical reviewer for this application was Dr. Christopher Toscano, with Dr. Lois Freed performing a secondary review.

The key findings from the nonclinical review are summarized below:

Pharmacology:

- Lecanemab binds to amyloid protofibrils and fibrillar amyloid beta. *In vitro*, lecanemab binds with higher affinity to amyloid beta protofibrils that to amyloid beta monomers. The rodent surrogate of lecanemab, mAb158, decreased the burden of amyloid protofibrils in the brain of transgenic rodent models (Tg2576 and APP_{ArcSwe}) that overexpress Aβ.

Toxicology

- The toxicology of lecanemab was adequately assessed in general toxicity studies in rats and monkeys. Single-dose studies were conducted in rats and repeated-dose studies in monkeys. Repeated-dose general toxicology studies in rodents were not feasible because of the formation of anti-lecanemab antibodies.

- In the single-dose toxicology study in rats, a single intravenous injection was administered up to the maximum feasible dose of 100 mg/kg. No adverse lecanemab-related findings were observed in this study.
- In a 4-week intravenous toxicology study conducted in monkeys administered a daily dose up to 50 mg/kg, no adverse lecanemab-related findings were observed.
- In a 39-week intravenous toxicology study conducted in monkeys administered a maximum feasible dose of 100 mg/kg once weekly, no adverse lecanemab-related findings were observed.

Reproductive and developmental toxicology

- These were considered to be unnecessary, based on the age range of the clinical population.

Genotoxicity

- Genotoxicity studies were not conducted because such studies are generally not required for antibodies.

Carcinogenicity

- Carcinogenicity studies were not conducted as repeat-dose toxicology studies were not feasible in rodents based on the formation of anti-lecanemab monoclonal antibodies.

Microhemorrhage

- In studies specifically conducted with mAb158 to microhemorrhage in Tg2576 and APP_{ArcSwe} transgenic mice, no mAb158-related microhemorrhage was seen.

Tissue Cross Reactivity

- Except for extracellular binding to amyloid plaques, all binding in the tissue cross-reactivity study was to cytosolic and thus not clinically relevant.

Dr. Toscano and Dr. Freed have concluded that the nonclinical data are adequate to support the approval of lecanemab for the treatment of AD.

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., 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.

OCP notes the following key review issues and conclusions:

- The effectiveness of lecanemab is supported by the exposure-response relationships from Study 201 on primary and secondary clinical endpoints and biomarker data.
- The recommended starting and maintenance dose is 10 mg/kg administered as an intravenous infusion over approximately one hour, once every two weeks.
- No dose adjustment is needed based on intrinsic and extrinsic factors.
- Lecanemab exposure following intravenous administration of the 2 formulations (Process (b) (4) and Process (b) (4)) used in the clinical studies were comparable, with an estimated relative bioavailability ((b) (4)) of 99.8%.
- The OCP review refers to the CMC review about the analytical comparability between the processes used in clinical studies (Processes (b) (4) and (b) (4)) and the to-be-marketed product (Process (b) (4)).
- In Study 201 Core, 63/154 (40.9%) of LEQEMBI-treated patients (10 mg/kg biweekly) 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.
- As a humanized IgG1 monoclonal antibody, lecanemab is expected to be degraded by proteolytic enzymes into small peptides and amino acids via catabolic pathways in the same manner as endogenous IgGs.
- No formal QT evaluation has been conducted for lecanemab. As a large molecule, lecanemab has a low likelihood to directly interact with ion channels.

The OCP team recommends a PMR to develop improved and validated assays of ADA and Nab to evaluate their impact on the pharmacokinetics, pharmacodynamics, safety, and efficacy of lecanemab.

The OCP review team recommends accelerated 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 Kun Jin, Ph.D., Team Leader and James (Hsien-Ming) Hung, Ph.D., Division Director.

The efficacy of lecanemab for this application was based on an analysis of change from baseline to Week 79 in brain amyloid plaque as measured by ^{18}F-florbetapir PET and quantified by a composite standardized uptake value ratio (SUVR) in Study 201.

Study 201 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. The study employed Bayesian response adaptive randomization, which allows for interim analyses during the study to update randomization allocation based on clinical endpoint results. Randomization was stratified by clinical subgroups (MCI due to Alzheimer's disease and mild Alzheimer's disease dementia), ApoE ε4 carrier status (carrier or non-carrier), and ongoing treatment with concurrent medications for treatment of Alzheimer's disease. The study included a 2-month screening period, an 18-month (78-week) placebo-controlled treatment period, and a safety follow-up period of 3 months after the final dose. For the placebo-controlled period, patients were randomized to placebo or one of 5 lecanemab dosing regimens according to the response adaptive randomization algorithm.

An open-label extension (OLE) phase of the study was initiated after analysis of the placebo-controlled portion of the study. Patients meeting the inclusion/exclusion criteria for the OLE and opting to enroll received lecanemab 10 mg/kg biweekly. The gap period in which patients were off treatment between the placebo-controlled portion and the OLE, ranged from 9 to 59 months, with a mean of 24 months.

Study Population

Study 201 enrolled patients age 50 to 90 years who 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), with evidence of brain Aβ pathology by either visual read of a positron emission tomography (PET) scan or CSF assessment of $A\beta_{1-42}$. Patients 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. Patients were excluded for any neurologic condition (other than AD) contributing to cognitive impairment, history of transient ischemic attacks, stroke, or seizures, presence of a bleeding disorder that is not under control, or uncontrolled Type 1 or Type 2 diabetes or hypertension. Patients 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.

Clinical Endpoints

The primary endpoint was the change from baseline in Alzheimer's Disease Composite Score (ADCOMS) at Week 53. The ADCOMS is a weighted linear combination of 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. ADAS-Cog 14 and CDR-SB were included as secondary endpoints.

Surrogate Endpoint

Change from baseline in brain amyloid plaque as measured by ^{18}F-florbetapir PET and quantified by a composite SUVR was assessed in a subset of patients at Week 53 and Week 79 and listed as a key secondary endpoint in the protocol. The primary amyloid PET analysis was the SUVR calculated for a composite cortical region of interest with whole cerebellum mask as a reference region. Different reference regions (subcortical white matter, derived whole cerebellum and adjusted by subcortical white matter, whole cerebellum mask and adjusted by subcortical white matter, derived whole cerebellum, cerebellar gray matter, and composite reference region) were also assessed and used for sensitivity analyses.

The Division has previously determined in the review of aducanumab that a reduction in amyloid plaque burden measured by PET imaging is reasonably likely to predict clinical benefit. Amyloid plaque is an underlying, fundamental, and defining pathophysiological feature of Alzheimer's disease. Although the role of amyloid and its relationship to other pathophysiological features of Alzheimer's disease, such as tau and neurodegeneration, is complicated, the presence of amyloid plaques is a primary and essential finding in Alzheimer's disease, including early in the disease. It is reasonable to conclude that treatment that is targeted at reducing amyloid plaque, and that successfully accomplishes that reduction, has the potential to convey clinical benefit.

Dosing

IV infusions of lecanemab or placebo were administered over approximately 60 minutes. Patients were randomized to receive placebo or 1 of 5 lecanemab treatment regimens, including 3 arms with biweekly (once every 2 weeks) dosing (2.5, 5, and 10 mg/kg) and 2 arms with monthly (once every 4 weeks) dosing (5 and 10 mg/kg). To maintain the blind, patients assigned to once every 4-week dosing regimens also received placebo infusions at intervening 2-week time points. Please refer to Dr. Krudys's review for a detailed description of the Bayesian response adaptive randomization that was used to allocate patients to treatment groups.

During the study the DSMB recommended that the 10 mg/kg biweekly dose no longer be administered to homozygous ApoE ε4 carriers due to emerging data from the study indicating a higher risk of ARIA in these patients. This modification was implemented in Protocol Amendment 4. Following discussion with European Health Authorities, it was decided that all ApoE ε4 carriers (homozygous and heterozygous) should no longer be administered lecanemab 10 mg/kg biweekly. Per Protocol Amendment 5 all ApoE ε4 carriers who had been receiving lecanemab 10 mg/kg biweekly for 6 months or less were discontinued from study drug and newly enrolled ApoE ε4 carriers were randomized to placebo or a lecanemab dose other than 10 mg/kg biweekly. Patients who were randomized to the 10 mg/kg biweekly dosing regimen and had been on treatment for more than 6 months were allowed to continue in the study.

All patients in the OLE received open-label lecanemab 10 mg/kg biweekly, including patients who were ApoE ε4 carriers.

Dose modifications/discontinuations for ARIA

Study drug was discontinued in all patients with ARIA-E and in patients who developed any macrohemorrhages greater than 10 mm, an area of superficial siderosis, or symptomatic treatment-emergent microhemorrhages. There were no dose reductions and no resumption of dosing after resolution of ARIA-E or ARIA-H. Administration of study drug was also to be terminated for infusion reactions of Grade 3 severity or above as defined in the National Cancer Institute – Common Terminology Criteria for Adverse Events (NCI-CTCAE), clinical features indicating meningoencephalitis, or hypersensitivity reactions with clinical features of tissue injury.

Statistical Analysis Plan:

Surrogate Endpoint

Change from baseline in brain amyloid plaque as measured by PET was analyzed with a mixed effects model with repeated measures (MMRM) with treatment group, visit, clinical subgroup (MCI due to Alzheimer's disease or mild Alzheimer's disease dementia), presence or absence of Alzheimer's disease medication use at baseline, ApoE ε4 status (carrier or non-carrier), region (North America, Western Europe, and Asia), and treatment group-by-visit interaction as fixed effects and baseline amyloid plaque level as a covariate. The adjusted p-value based on the Dunnett-Hsu method with 1-sided alpha of 0.05 was provided in addition to the p-value corresponding to pairwise comparison.

Clinical Endpoints

The primary analysis of the change from baseline to Week 53 in the ADCOMS was based on Bayesian statistics. For each dose the probability of being superior to placebo was determined by comparing the posterior distribution of the mean change from baseline to Week 53 between the lecanemab treatment arm and placebo. The threshold for success of the primary endpoint was a probability of at least 0.80 that the target dose was superior to placebo by 25%. The same Bayesian analysis was repeated for change from baseline in ADCOMS to Week 79 as well as for CDR-SB and ADAS-Cog 14.

Change from baseline in clinical endpoints was also assessed with MMRM with treatment group, visit, clinical subgroup, presence or absence of Alzheimer's disease medication use at baseline, ApoE ε4 status, region, and treatment group-by-visit interaction as fixed effects and clinical scale at baseline as a covariate. The analyses censored patients at the time of initiation of new Alzheimer's disease medication or dose adjustment of an existing stable treatment of an Alzheimer's disease medication. There was no adjustment for multiplicity.

Subgroup Analyses

Subgroup analyses for amyloid PET and clinical endpoints were planned for the following pre-defined groups:

- Age (≤64, 65-79, ≥80)
- Gender (male, female)
- Ethnicity
- Race
- Region (North America, Western Europe, and Asia)
- Clinical subgroup (MCI due to Alzheimer's disease or mild Alzheimer's disease dementia)
- ApoE ε4 carrier status (carrier or non-carrier)
- Presence or absence of Alzheimer's disease medication use

Results

Of the 3267 patients who signed the informed consent form at screening, a total of 856 continued in the study to randomization. Table 1 contains information regarding demographic and disease characteristics for each treatment arm in the Full Analysis Set. The proportion of ApoE ε4 carriers was unbalanced due to the protocol amendments restricting enrollment of ApoE ε4 carriers in the 10 mg/kg biweekly lecanemab treatment arm. ApoE ε4 carriers were more likely to be allocated by the Bayesian RAR to the next most likely efficacious doses of 10 mg/kg monthly and 5 mg/kg biweekly. There was also a higher proportion of patients with mild Alzheimer's disease dementia in the 10 mg/kg biweekly treatment arm compared to placebo and more male patients in the 10 mg/kg monthly and 10 mg/kg biweekly treatment arms compared to placebo. The population enrolled in the study is generally representative of the patient population except for an under-representation of African American and Hispanic patients. Overall, 80% of patients were enrolled in the United States.

Table 1: Study 201 Baseline Demographic and Disease Characteristics (Full Analysis Set)

Demographic Parameters	**Placebo** (N=238) n (%)	**Treatment Group**					
		2.5 mg/kg biweekly (N=52) n (%)	**5 mg/kg monthly** (N=48) n (%)	**5 mg/kg biweekly** (N=89) n (%)	**10 mg/kg monthly** (N=246) n (%)	**10 mg/kg biweekly** (N=152) n (%)	**Total** (N=825) n (%)
Sex							
Male	101 (42%)	26 (50%)	24 (50%)	41 (46%)	136 (55%)	88 (58%)	416 (50%)
Female	137 (58%)	26 (50%)	24 (50%)	48 (54%)	110 (45%)	64 (42%)	409 (50%)
Age							
Mean years (SD)	71.1 (8.9)	70.5 (8.3)	70.4 (7.5)	70.6 (7.4)	71.3 (7.5)	72.6 (8.8)	71.3 (8.2)
Median (years)	72	70.5	71	72	71	73	72
Min, max (years)	50, 89	50, 86	55, 84	52, 87	53, 90	51, 88	50, 90
Baseline Clinical Stage							
MCI due to AD	154 (65%)	34 (65%)	33 (69%)	52 (58%)	166 (68%)	90 (59%)	529 (64%)
Mild AD	84 (35%)	18 (35%)	15 (31%)	37 (42%)	80 (32%)	62 (41%)	296 (36%)
Laboratory ApoE ε4 Status							
Carrier	169 (71%)	38 (73%)	37 (77%)	81 (91%)	218 (89%)	46 (30%)	589 (71%)
Heterozygote	129 (54%)	33 (64%)	26 (54%)	67 (75%)	160 (65%)	38 (25%)	453 (55%)
Homozygote	40 (17%)	5 (10%)	11 (23%)	14 (16%)	58 (24%)	8 (5%)	136 (17%)
Non-carrier	69 (29%)	14 (27%)	11 (23%)	8 (9%)	28 (11%)	106 (70%)	236 (29%)
Baseline CDR-SB							
Mean (SD)	2.9 (1.5)	3.0 (1.6)	2.9 (1.4)	3.0 (1.3)	2.9 (1.3)	3.0 (1.4)	2.9 (1.4)
Median	3	3	2.5	3	2.5	3	3
Min, Max	0.5, 9	0.5, 7	1, 6	0.5, 6.5	0.5, 8	0.5, 8.5	0.5, 9
Baseline MMSE							
<22	0	0	0	0	1 (<1%)	0	1 (<1%)
≥22 - <27	135 (57%)	32 (62%)	32 (67%)	55 (62%)	150 (61%)	88 (58%)	492 (60%)
≥27 - ≤30	103 (43%)	20 (38%)	16 (33%)	34 (38%)	95 (39%)	64 (42%)	332 (40%)
Concomitant AD medication							
Cholinesterase inhibitors and/or memantine at baseline	128 (54%)	28 (54%)	25 (52%)	56 (63%)	131 (53%)	79 (52%)	447 (54%)
Region							
United States	183 (77%)	46 (88%)	39 (81%)	63 (71%)	201 (82%)	130 (86%)	662 (80%)
Canada	12 (5%)	1 (2%)	2 (4%)	7 (8%)	14 (6%)	5 (3%)	41 (5%)
Western Europe	28 (12%)	4 (8%)	6 (13%)	7 (8%)	15 (6%)	10 (6%)	70 (9%)
Asia	15 (6%)	1 (2%)	1 (2%)	12 (13%)	16 (6%)	7 (5%)	52 (6%)

Source: Tables 14.1.4.1.1 and 14.1.4.1.2 in Study 201 CSR

Surrogate Endpoint

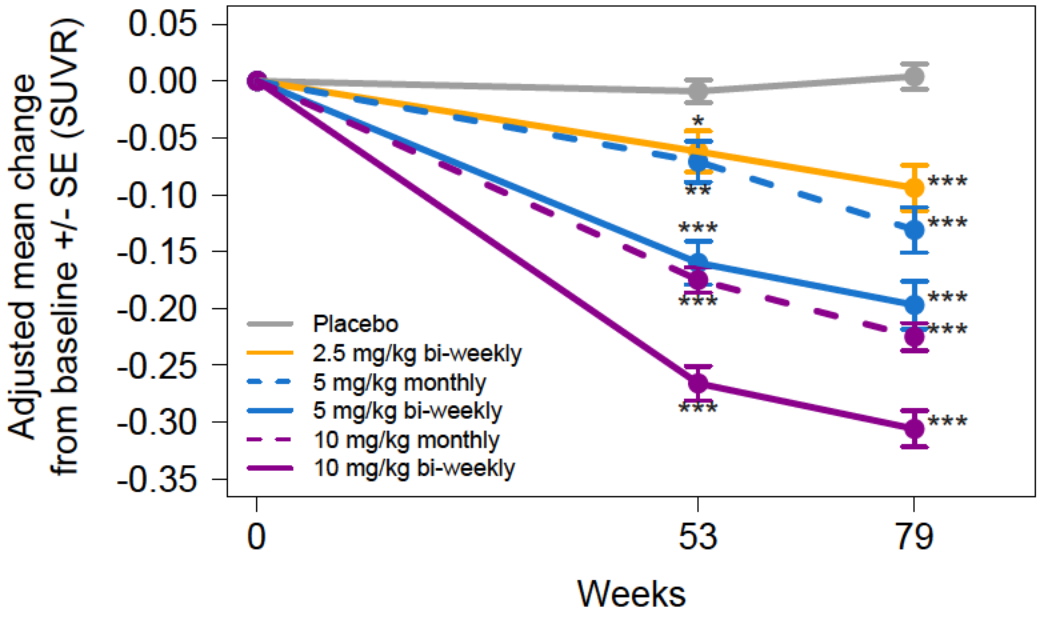
Lecanemab treatment demonstrated a statistically significant treatment effect on the surrogate endpoint of change from baseline in brain amyloid as measured by ^{18}F-florbetapir PET and quantified by a composite SUVR at Week 79 for all regimens, including the proposed dosing regimen of 10 mg/kg biweekly (-0.310, p<0.001) (Table 2). The results indicate time- and dose-dependent relationships for reduction of brain amyloid with lecanemab treatment (Figure 1). Consistent and statistically significant findings were observed using all other reference regions (subcortical white matter, derived whole cerebellum and adjusted by subcortical white matter, whole cerebellum mask and adjusted by subcortical white matter, derived whole cerebellum, and composite reference region). Changes in brain amyloid as measured by PET were also calculated using the Centiloid scale. The change from baseline in brain amyloid at Week 79 compared to placebo for 10 mg/kg biweekly regimen was -73.5 Centiloids (p<0.001). Please refer to Dr. Krudys's review for complete Centiloid results.

Table 2: Study 201 Surrogate Endpoint Analysis (SUVR)

	Placebo (N=99)	**2.5 mg/kg biweekly** (N=28)	**5 mg/kg monthly** (N=28)	**5 mg/kg biweekly** (N=27)	**10 mg/kg monthly** (N=89)	**10 mg/kg biweekly** (N=44)
Baseline SUVR						
n	98	28	27	27	88	44
Mean (SD)	1.40 (0.16)	1.41 (0.11)	1.42 (0.17)	1.40 (0.12)	1.42 (0.18)	1.37 (0.16)
Min, max	0.91, 1.73	1.11, 1.60	1.09, 1.72	1.23, 1.70	1.04, 1.84	0.99, 1.77
Change from Baseline in SUVR at Week 53						
n	96	27	27	25	88	43
Least square mean	-0.009	-0.062	-0.071	-0.160	-0.175	-0.266
Standard error	0.010	0.018	0.018	0.019	0.011	0.015
Difference from placebo		-0.053	-0.062	-0.151	-0.167	-0.257
90% CI for difference		(-0.086, -0.019)	(-0.096, -0.029)	(-0.185, -0.117)	(-0.189, -0.144)	(-0.287, -0.227)
p-value (compared with placebo)		0.010	0.002	<0.001	<0.001	<0.001
Dunnett p-value		0.100	0.027	0.000	0.000	0.000
Change from Baseline in SUVR at Week 79						
n	88	23	23	24	82	37
Least square mean	0.004	-0.094	-0.131	-0.197	-0.225	-0.306
Standard error	0.011	0.020	0.020	0.021	0.012	0.016
Difference from placebo		-0.099	-0.136	-0.201	-0.229	-0.310
90% CI for difference		(-0.136, -0.061)	(-0.173, -0.098)	(-0.238, -0.164)	(-0.254, -0.204)	(-0.344, -0.277)
p-value (compared with placebo)		<0.001	<0.001	<0.001	<0.001	<0.001
Dunnett p-value		0.000	0.000	0.000	0.000	0.000

Source: Tables 25 and 14.2.2.3.2e in Study 201 CSR

Figure 1: Study 201 Change from Baseline in Brain Amyloid (SUVR)



Placebo	n=98	96	88
2.5 mg/kg bi-weekly	n=28	27	23
5 mg/kg monthly	n=27	27	23
5 mg/kg bi-weekly	n=27	25	24
10 mg/kg monthly	n=88	88	82
10 mg/kg bi-weekly	n=44	43	37

Created by the reviewer from 14.2.2.3.2e in Study 201 CSR
*p<0.05, **p<0.01. ***p<0.001

Reduction of brain amyloid plaque with lecanemab treatment was also demonstrated in patients who were randomized to placebo in the double-blind portion of the study and subsequently treated with lecanemab 10 mg/kg biweekly in the open-label extension.

Subgroup analyses demonstrated that significant amyloid plaque reduction was observed across patient demographics and disease characteristics.

Primary Endpoint

The primary Bayesian analysis of ADCOMS at Week 53 indicated that the lecanemab 10 mg/kg biweekly dosing regimen had a 64% probability of being superior to placebo by 25%, which did not meet the prespecified criterion for success of 80% probability. The probability of lecanemab 10 mg/kg biweekly being superior to placebo by any amount at Week 53 was 98%.

The original clinical study report included a table suggesting there was a (b) (4) % probability of the 10 mg/kg biweekly dosing regimen being superior to placebo by 25% on ADCOMS at Week 53. An addendum to the clinical study report clarified that this table was incorrectly inserted in the original report and presented results of a sensitivity analysis without

censoring efficacy data based on initiation or dose adjustment of Alzheimer's disease medications. According to the SAP, the primary analysis was to be performed censoring efficacy data based on initiation or dose adjustment of Alzheimer's disease medications. This primary analysis resulted in a probability of 64% of the 10 mg/kg biweekly regimen being superior to placebo by 25%.

Secondary Clinical Endpoints

Assessment of clinical endpoints at Week 79 were prespecified as key secondary objectives of the study. A summary of the MMRM analysis results for the key secondary endpoints at Week 79 is provided in Table 3. The 10 mg/kg biweekly lecanemab treatment regimen demonstrated favorable numerical results for ADCOMS and CDR-SB and nominal statistical significance for ADAS-Cog 14 at Week 79.

Table 3: Study 201 Secondary Clinical Endpoint Analysis (Full Analysis Set, Week 79)

	Placebo (N=238)	**2.5 mg/kg biweekly** (N=52)	**5 mg/kg monthly** (N=48)	**5 mg/kg biweekly** (N=89)	**10 mg/kg monthly** (N=246)	**10 mg/kg biweekly** (N=152)
Baseline ADCOMS						
N	238	52	48	89	246	152
Mean	0.370	0.386	0.395	0.390	0.373	0.373
Change from Baseline in ADCOMS at Week 79						
n	160	33	35	61	146	79
LS mean	0.193	0.173	0.192	0.199	0.166	0.136
Standard error	0.017	0.035	0.035	0.026	0.018	0.022
Difference from placebo		-0.020	-0.001	0.006	-0.028	-0.057
90% CI for difference		(-0.083, 0.042)	(-0.064, 0.061)	(-0.044, 0.055)	(-0.065, 0.010)	(-0.102, -0.013)
p-value (compared with placebo)		0.59	0.97	0.86	0.23	0.03
Baseline CDR-SB						
n	238	52	48	89	246	152
Mean	2.89	2.98	2.94	3.03	2.91	2.97
Change from Baseline in CDR-SB at Week 79						
n	161	34	36	67	149	84
LS mean	1.50	1.23	1.71	1.46	1.25	1.10
Standard error	0.16	0.34	0.33	0.25	0.17	0.21
Difference from placebo		-0.27	0.21	-0.04	-0.25	-0.40
90% CI for difference		(-0.88, 0.33)	(-0.38, 0.81)	(-0.51, 0.44)	(-0.61, 0.11)	(-0.82, 0.03)
p-value (compared with placebo)		0.46	0.56	0.90	0.26	0.13
Baseline ADAS-Cog 14						
n	237	52	47	89	246	152

Mean	22.56	22.72	22.94	22.75	21.90	22.06
Change from Baseline in ADAS-Cog 14 at Week 79						
n	158	33	34	61	146	79
LS mean	4.90	5.57	5.75	4.51	4.62	2.59
Standard error	0.62	1.28	1.28	0.96	0.65	0.81
Difference from placebo		0.67	0.84	-0.40	-0.28	-2.31
90% CI for difference		(-1.59, 2.93)	(-1.42, 3.11)	(-2.20, 1.40)	(-1.64, 1.08)	(-3.91, -0.72)
p-value (compared with placebo)		0.62	0.54	0.72	0.74	0.02

Source: Tables 27, 30, 36, 38, 43, and 45 in Study 201 CSR
All p-values are nominal.

Dr. Krudys notes the concerns about the interpretation of the clinical efficacy data which were conveyed at the 2018 End of Phase 2 Meeting, including the proportion of patients with missing efficacy data, the use of ADCOMS as the primary endpoint, statistical issues with multiplicity, and the disproportion of ApoE ε4 between the lecanemab 10 mg/kg biweekly arm and placebo, but ultimately concludes that in the context of an application for accelerated approval, the generally consistent and favorable results on clinical endpoints support the reasonable likelihood of the surrogate endpoint to predict clinical benefit.

Pharmacodynamic Endpoints

Plasma Aβ42/40 ratio was evaluated in 284 patients (including 88 in the placebo arm and 43 in the 10 mg/kg biweekly lecanemab treatment arm). The applicant reports a dose- and time-dependent increase in plasma Aβ42/40 ratio with LS mean changes at Week 79 for placebo and 10 mg/kg lecanemab biweekly of 0.0021 and 0.0075, respectively (LS mean difference of 0.0054, $p<0.004$).

Plasma p-tau 181 was evaluated in 562 patients (including 179 in the placebo arm and 84 in the 10 mg/kg biweekly lecanemab treatment arm). The applicant reports a dose-dependent decrease in plasma p-tau 181 with LS mean changes at Week 79 for placebo and 10 mg/kg lecanemab biweekly of 0.083 pg/ml and -1.11 pg/ml, respectively (LS mean difference of -1.20 pg/ml, $p<0.001$). No effect was observed on plasma neurofilament light chain (NfL).

A total of 656 patients (including 209 in the placebo arm and 99 in the 10 mg/kg biweekly lecanemab treatment arm) had sufficient vMRI data to derive at least one parameter. There was no notable treatment difference in change from baseline in total hippocampus volume. The LS mean changes at Week 79 for placebo and 10 mg/kg lecanemab biweekly were -257 mm^3 and -277 mm^3 (LS mean difference of -19 mm^3, $p=0.24$).

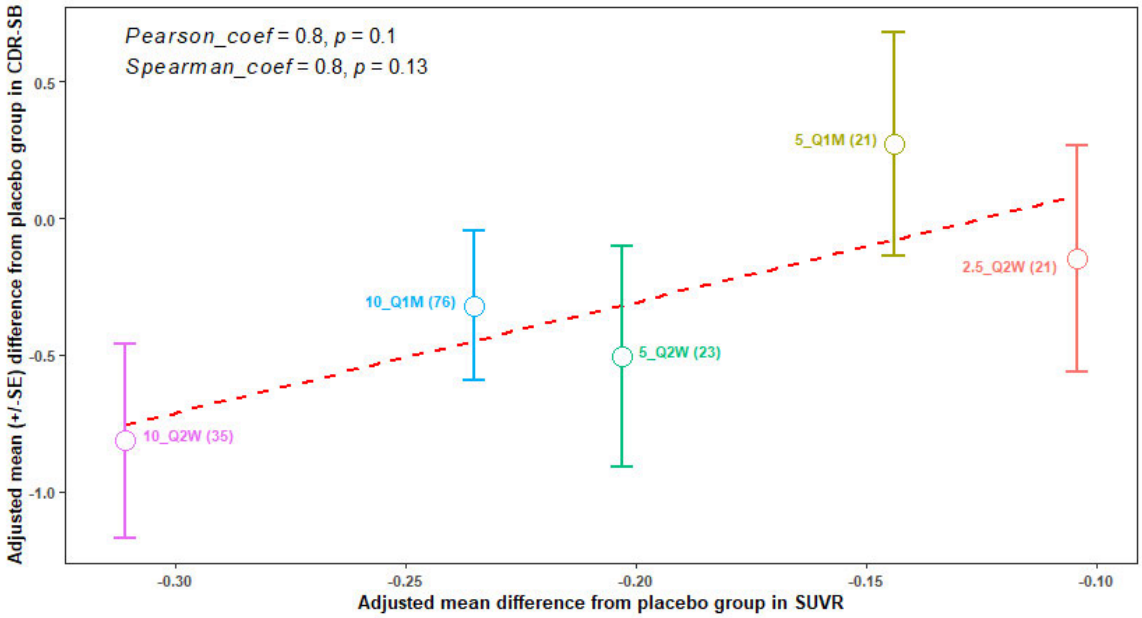
Lecanemab treatment was associated with a decrease in whole brain volume with LS mean changes at Week 79 for placebo and 10 mg/kg lecanemab biweekly of -21776 mm^3 and -

29894 mm^3 (LS mean difference of -8118 mm^3, p<0.001) and an increase in total ventricular volume with LS mean changes at Week 79 for placebo and 10 mg/kg lecanemab biweekly of 5345 mm^3 and 7662 mm^3 (LS mean difference of 2318 mm^3, p<0.001). Given the favorable results on clinical endpoints observed in Study 201 and the clinical benefit publicly reported in Study 301, Dr. Krudys questions the clinical relevance of the changes to whole brain volume and total ventricular volume. Dr. Krudys also notes that fluid biomarkers of neurodegeneration, including plasma NfL in Study 201 and reported markers in Study 301, do not suggest a greater extent of neurodegeneration with lecanemab treatment.

Relationship between Amyloid PET and Clinical Endpoints

The correlation between the effect on amyloid PET and the effect on clinical endpoints was explored at the dose level in the subpopulation of patients who had post-baseline assessments for both endpoints. A decrease in brain amyloid was associated with treatment effects at the population level for ADCOMS (Pearson correlation coefficient=0.832, p=0.08), CDR-SB (Person correlation coefficient=0.805, p=0.10) (Figure 2), and ADAS-Cog14 (Person correlation coefficient=0.699, p=0.189).

Figure 2: Correlation between Change from Baseline in CDR-SB and Amyloid PET SUVR at Week 79



Source: Clinical Pharmacology Review

A mediation analysis was also performed by the applicant to investigate the link between the effect of lecanemab on brain amyloid and clinical endpoints. In the mediation analysis, the proportion of treatment effect explained by amyloid PET SUVR was defined as the percentage change of treatment effects estimated from two ANCOVA models with or without adjusting for amyloid PET SUVR. For the 10 mg/kg biweekly dose arm, the estimated treatment effect on CDR-SB changed from -0.63 (p=0.11) to -0.03 (p=0.95) using ANCOVA and after adjusting

for the change from baseline in amyloid PET SUVR. The proportion of the treatment effect explained by amyloid PET SUVR is therefore 95%, suggesting a relationship between amyloid PET SUVR and the treatment effect on CDR-SB.

Biostatistics Review Conclusions

Dr. Massie noted that the analysis plan for Study 201 did not control for type I error at the required level of 0.05 two-sided due to the interim analyses without any multiplicity correction and therefore the study is considered to be exploratory. Nevertheless, the study failed to achieve the prespecified criterion for success. Dr. Massie acknowledges the extremely low p-values for the PET SUVR endpoint but cautions that these results should be considered exploratory. Dr. Massie further expresses uncertainty whether the treatment effect on amyloid is reasonably likely to predict change on the clinical outcome because, e.g., there is no apparent clinical endpoint treatment effect in ApoE ε4 non-carriers despite having amyloid reductions comparable to ApoE ε4 carriers.

Efficacy Conclusions

The applicant has submitted data to support the accelerated approval of lecanemab for the treatment of Alzheimer's disease based on a surrogate endpoint, the reduction in amyloid plaque burden measured by PET imaging, which has been previously found by the Agency to be reasonably likely to predict clinical benefit. The applicant has conducted an adequate and well-controlled study, 201, that demonstrated a robust and statistically significant treatment effect for the 10 mg/kg biweekly dose of lecanemab on brain amyloid plaque as measured by PET and quantified by a composite standard uptake value ratio (SUVR) in a subset of patients at Week 53 and Week 79. The lecanemab 10 mg/kg biweekly arm had a statistically significant reduction in brain amyloid plaque from baseline to Week 79 compared to the placebo arm (mean difference of -0.31 SUVR or -73.5 Centiloids; $p<0.001$). Lecanemab reduced brain amyloid plaque in a dose- and time-dependent manner. These findings were supported by the primary analysis of ADCOMS at Week 53 indicated that the lecanemab 10 mg/kg biweekly dosing regimen had a 64% probability of being superior to placebo by 25%. Prespecified analyses of data at Week 79 suggested reduced decline on clinical endpoints by approximately 20% to 40%, as well as a reduced decline on other clinically meaningful outcome measures.

The clinical reviewer, Dr. Krudys, has concluded that the applicant has provided substantial evidence of effectiveness to support accelerated approval. He has determined that results of Study 201 on an acceptable surrogate endpoint that is reasonably likely to predict clinical benefit are robust and persuasive, and that Study 201 can be considered a single adequate and well-controlled trial that is capable of providing substantial evidence of effectiveness. The clinical pharmacology review team also supports approval of the application and notes that the effectiveness of lecanemab is supported by the exposure-response relationships from Study 201 on primary and secondary clinical endpoints and biomarker data. The biostatistics reviewer, Dr. Massie, acknowledges the extremely low p-values for the PET SUVR endpoint but cautions that these results should be considered exploratory given that the

analysis plan for Study 201 did not control for type I error at the required level of 0.05 two-sided due to the interim analyses without any multiplicity correction. Dr. Massie further expresses uncertainty whether the treatment effect on amyloid is reasonably likely to predict change on the clinical outcome because, e.g., there is no apparent clinical endpoint treatment effect in ApoE ε4 non-carriers despite having amyloid reductions comparable to ApoE ε4 carriers.

The Division notes the issues that Dr. Massie has raised but, overall, the findings on brain Aβ plaque appear robust and persuasive despite the concerns for lack of type I error control. There are limitations on the ability to interpret subgroup analyses by ApoE ε4 status given the small numbers of patients. Although not yet submitted to the Agency for review, it is also notable that the topline results of Study 301 that have been publicly reported appear to support the clinical benefit of Aβ plaque reduction; however, that study showed more robust results in ApoE ε4 non-carriers than in carriers.

The Agency has previously found, with the accelerated approval of aducanumab, that reduction of brain Aβ plaque on PET is reasonably likely to predict clinical benefit in Alzheimer's disease. This determination was based on the character of brain Aβ plaque as an underlying, fundamental, and defining pathophysiological feature of the disease, and modeling that demonstrated a clear exposure-response relationship between reduction of brain Aβ plaque and preservation of clinical function that was consistent across aducanumab and all 6 other available programs of anti-amyloid beta antibodies under development over the past decade based on a review of publicly available information. The current data from lecanemab in Study 201 also support the use of the reduction of brain Aβ plaque on PET as a surrogate endpoint reasonably likely to predict clinical benefit.

The accelerated approval provisions in section 506(c) of the FD&C Act (as amended by FDASIA) provide that FDA may grant accelerated approval to: . . . a product for a serious or life-threatening disease or condition . . . upon a determination that the product has an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit, or on a clinical endpoint that can be measured earlier than irreversible morbidity or mortality, that is reasonably likely to predict an effect on irreversible morbidity or mortality or other clinical benefit, taking into account the severity, rarity, or prevalence of the condition and the availability or lack of alternative treatments.

With regard to the evidence of effectiveness supporting accelerated approval on the basis of a reduction in amyloid beta plaque, the requirements are met. Study 201 was an adequate and well-controlled study that demonstrated clear and persuasive highly statistically significant dose- and time-dependent reductions of Aβ plaque on PET imaging, a surrogate endpoint that has been determined to be reasonably likely to predict clinical benefit. These findings are supported by a reduction in decline on clinical outcome measures in the study. Although not yet submitted to the Agency for review, it is also notable that the topline results of Study 301 that have been publicly reported appear to support the clinical benefit of Aβ plaque reduction. Given the robust, persuasive, and consistent effects of lecanemab on an

acceptable surrogate endpoint, brain Aβ plaque on PET, Study 201 can be considered a single adequate and well-controlled trial that provides substantial evidence of effectiveness. The applicant proposes to submit the data from Study 301 as soon as possible to fulfill the requirement to confirm the benefit the clinical benefit of lecanemab for the treatment of Alzheimer's disease.

Lecanemab will be indicated for the treatment of Alzheimer's disease; however, the indication statement will note that treatment should be initiated in 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 unblinded data from Study 201. Ongoing studies 301 Core and OLE, 303, and substudy A3 and A45s have enrolled 2106 subjects but only provide blinded data that do not contribute to the safety database. During the review, Study 301 Core was completed, and topline results were publicly released and published.[1] The data have not been formally submitted to the Agency for review and confirmation; however, the Division has considered these reported safety results in the context of our review and interpretation of the current the safety data. The safety database includes 763 subjects from Studies 101, 104, 201 Core, 201 OLE, and 004, exposed to at least one dose of lecanemab. At the proposed dose of 10 mg/kg biweekly (L, 237 patients were treated for at least 6 months and 217 were treated for at least 1 year, exclusive of the 9 to 56-month GAP period between the Core and OLE. Dr. Erten-Lyons notes that although the 1-year exposure meets the ICH E1 guideline for long -term treatment of non-life-threatening conditions for exposure of 100

[1] van Dyck CH. et al.. Lecanemab in Early Alzheimer's Disease. N Engl J Med. 2022 Nov 29. doi: 10.1056/NEJMoa2212948. Epub ahead of print.

patients at the clinically relevant dose, the ICH guidelines for drugs intended for long-term use of at least 300 patients for 6 months are not met. The 6-month numbers were provided in the meeting package for the Type B meeting held on September 10, 2021, for which the meeting minutes state that on face, the proposed safety database appears sufficient to support the submission of a marketing application for lecanemab. This was based on the Division's determination that Alzheimer's disease is a serious and life-threatening disease. The Division also considered that the larger number of 1-year exposures at one year offset the limitations of the smaller number of exposures at 6 months and one year. As of the 120-day safety update, 186 patients in the safety database of unblinded data have been exposed to at the proposed dose for at least 18 months.

Because of a higher risk of ARIA in ApoE ε4 carriers, a protocol change required discontinuation of ApoE ε4 carriers from the protocol if they had less than 6 months of treatment at the time of the change, and additional ApoE ε4 carriers were not randomized to the proposed dose. This resulted in exposure for ApoE ε4 carriers at the proposed dose of 49 total (30% of the 161 patients exposed to lecanemab 10 mg/kg biweekly in the Study 201 CORE Population), 18 subjects for at least 6 months, and 12 subjects for at least 12 months, limiting conclusions that can be made about safety in APOE e4 carriers at the proposed dose.

In Study 201 Core at the proposed dose, 88% of the population treated with the proposed dose were from North America. The mean and median age was approximately 73 years (range 51 to 88 years). Sixty-two percent (n=99) were 65 to less than 80 years old and 21% (n=34) were at least 80 years old. Forty-four percent were women. Six percent (10/161) of patients were ApoE ε4 homozygotes, 24% (39/161) were heterozygotes, and 70% (112/161) were noncarriers. White patients accounted for 93%, Hispanic or Latino accounted for 6%, 4% were Asian, and Black or African American accounted for 2%. The population demographics were similar across all dose groups, except for the presence of ApoE ε4 carriers that represented approximately 70 to 90% of the other dose groups. Dr. Erten-Lyons notes that women, Hispanic or Latino, and Black patients are under-represented compared to the general Alzheimer's disease population, and that patients with moderate or severe dementia due to Alzheimer's disease were not eligible for enrollment in Study 021. Therefore, the safety outcomes may underestimate the impact of adverse events in a broader population. Of note, demographics in the 201 OLE were similar to those in the CORE study, except that ApoE ε4 carriers represented approximately 69% of the 201 OLE population.

Dr. Erten-Lyons considered the applicant's translation of adverse events from verbatim terms to preferred terms to be adequate. The original submission had inconsistencies in collecting symptomatic ARIA events as treatment-emergent adverse events (TEAEs) captured in the CIOMS forms, case report forms, narratives, and the ADAE dataset. Subsequent to related information requests, Dr. Erten-Lyons noted that these issues were addressed with updated ADAE datasets. The original submission did not categorize severity of ARIA-H events using radiographic criteria, but subsequently reassigned severity ratings based on a radiographic rating system that the Division uses as a standard approach to that evaluation.

Deaths

Dr. Erten-Lyons does not identify any deaths attributable to treatment with lecanemab in 201 Core or in the OLE. She notes that in the placebo-controlled 201 Core study, there was not an excess of deaths in the lecanemab group across all doses (0.8%, 5/609) compared to placebo (0.8%, 2/245). There were 5 deaths in Study 201 OLE (2.8%). In 201 Core and OLE, Dr. Erten-Lyons notes no clusters of unusual deaths and that none of the deaths were preceded by ARIA. In ongoing blinded Study 301 Core and OLE, Dr. Erten-Lyons reports 12/1899 deaths (0.6%), none of which was preceded by documented ARIA, although 1 was an intracranial hemorrhage (subject (b) (6)) confirmed to be a patient receiving placebo in a December 14, 2022, response to an information request. There were no deaths reported in studies 101, 104, 004, or ongoing study 303. One additional death in ongoing 301 OLE was reported to the Agency on December 20, 2022 and reported in the journal, Science, on December 21, 2022, and is described below.

Dr. Erten-Lyons notes that the Agency became aware of two additional deaths due to intracerebral hemorrhage greater than 1 cm in the 301 OLE. One event occurred in (b) (6) in an 87-year-old male with a past medical history including atrial fibrillation, hyperlipidemia, coronary artery disease, lacunar stroke, and cerebral microhemorrhage, with current medications of donepezil, apixaban, and atorvastatin, as well as tamsulosin. The patient sustained a fall on Day 77 after 6 doses of study drug, followed by pneumonia, COVID, and an ulnar pseudoaneurysm treated with thrombin, and another fall from bed. A subsequent MRI on Day 116 showed a left occipital intracerebral hemorrhage (> 1 cm). Apixaban was stopped. This was followed by a myocardial infarction on Day 122 and TIA-like events on Day 126. The patient died on Day 144 due to the cardiopulmonary causes. As Dr. Erten-Lyons notes, the cerebral hemorrhage was likely related to use of apixaban and possibly the fall from the bed.

The second event occurred in a 65-year-old woman with MCI, homozygous for ApoE ε4, who completed 301 Core on placebo and enrolled in 301 OLE. This case has been recently published.[2,3] Four days after the third dose of lecanemab, the participant was noted to have 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. 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. 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. MRI performed 3 days after the CT scan showed extensive multicompartmental ICHs, innumerable hematomas, SAH and right intraventricular hemorrhage with 5 mm leftward midline shift and

[2] Reish NJ, Jamshidi P, Stamm B, et al. NEJM, January 4, 2023, DOI: 10.1056/NEJMc2215148
[3] Sabbagh M, van Dyck CH. NEJM, January 4, 2023. DOI: 10.1056/NEJMc2215907

bilateral uncal herniation. At the patient's directive, she was extubated and died eight days after the last dose of study drug. A subsequent autopsy was reported to show extensive, multi-focal intraparenchymal hemorrhage by gross pathology examination with microscopic examination demonstrating AD neuropathologic change and widespread necrotizing vasculitis involving blood vessels with cerebral amyloid angiopathy. Dr. Erten-Lyons notes that a large vessel stroke, thrombolysis and cerebral amyloid angiopathy are all associated with an increased risk of intracerebral hemorrhage which confound the ability to draw any conclusions on causality.

An additional notable report of death in the 301 OLE (Mfr. Control No. :EC-2022-123944(0), subject (b) (6)), was submitted to FDA on December 20, 2022, and reported in the journal, Science, on December 21, 2022.[4] This was a 79 year old female with early Alzheimer's disease who completed 301 Core on placebo and was enrolled in the OLE in (b) (6). The patient was homozygous for ApoE ε4. The patient received 3 doses of lecanemab 10 mg/kg every two weeks in the OLE. The last dose of study drug was administered on (b) (6). According to the CIOMS report, 1 week after the last dose the subject experienced a sudden onset of difficulty speaking, staring into space, and left side weakness, reported as a "possible CVA (cerebrovascular accident)" and "possible seizure". The subject was taken to an emergency department and was intubated and hospitalized. An MRI with and without contrast was reported as showing "no mass, no definite bleeding or edema or stroke". A prior MRI from (b) (6), was notable only for a "a previously noted left parietal < 1 cm meningioma". A seizure was suspected but no definite seizure activity was noted. It was reported that the subject had never been on anticoagulation during the study or in the hospital. The subject was extubated and 5 days after the original event, developed respiratory distress and passed away. According to the CIOMS report, the subject had risk factors for seizures, including underlying Alzheimer's disease, and for cerebrovascular disease, including advanced age, hyperlipidemia, aortic atherosclerosis, chronic kidney disease, and prediabetes. According to the CIOMS form, an autopsy was performed but results had not been reported to the investigator site. Descriptions of brain bleeding and swelling, treatment of the event with steroids, and multiorgan failure noted in the Science description, are not noted in the CIOMS form and have not been submitted to the Agency for review. The Agency has requested that the applicant provide additional information on the case, including MRI images and the autopsy report. The applicant has not been able to obtain additional information as of January 3, 2023. The confirmation of the events reported in the Science article and their relationship to study drug cannot be determined at this time; however, the available information does not change the risk-benefit assessment for this review.

Dr. Erten-Lyons notes that the incidence of death by person-years of exposure to lecanemab 10 mg/kg biweekly in 201 Core and OLE is 9.3/1,000 person years (10/1073 person years) 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

[4] https://www.science.org/content/article/scientists-tie-third-clinical-trial-death-experimental-alzheimer-s-drug

population with early-stage Alzheimer's disease (mild cognitive impairment and mild dementia) with the overall Alzheimer's disease population inclusive of later stages. It is also reported that there was no imbalance in deaths in deaths in the 301 Core study; however, the Division is not able to confirm those results at this time.

Serious and Significant Adverse Events

In the placebo-controlled Study 201 Core, serious adverse events (SAEs) occurred in 13% (21/161) of lecanemab 10 mg/kg biweekly -treated patients and in 17.1% (42/245) of placebo-treated patients. The most frequently reported SAEs included 3 patients with ARIA-E events (2% for lecanemab 10 mg/kg biweekly vs. 0 in placebo), arthralgia (1.2% for lecanemab 10 mg/kg biweekly vs. 0 in placebo), and cerebral microhemorrhage (ARIA-H) that occurred in 2 patients (1.2%) for lecanemab 10 mg/kg biweekly vs. none in placebo. In the 201 OLE, SAEs occurred in 24.4% (44/180) patients. The most frequently occurring SAEs in the OLE were transient ischemic attack, acquired epileptic aphasia/ generalized tonic-clonic seizures, and acute kidney injury that each occurred in 3 patients. One patient in the OLE study had pancytopenia, with bone marrow biopsy consistent with post-myeloproliferative neoplasm acute myeloid leukemia (AML), after the 57th dose of study drug on day 855; Dr. Erten-Lyons notes that the patient had a history of essential thrombocytopenia that can develop into AML. Dr. Erten Lyons notes 2 treatment emergent seizures within 30 days after a dose in 201 Core reported as SAEs (1 in lecanemab 5 mg/kg biweekly and 1 in lecanemab 10 mg/kg monthly) and no seizure SAEs in placebo. These were 1 in the lecanemab 5 mg/kg biweekly group 14 days after a dose and 1 in the lecanemab 10 mg/kg monthly group 8 days after a dose, both of which occurred in the setting of risk factors including a ventriculo-peritoneal shunt placement, hyponatremia, and hypokalemia. One poorly documented seizure, not reported or confirmed by a medical professional, reportedly occurred in a patient on the way to the hospital, in the setting of radiographically severe ARIA on lecanemab 10 mg/kg biweekly (Subject (b) (6)).

Dr. Erten-Lyons identified several SAEs of intracranial hemorrhage. These include: an SAE of intracerebral hemorrhage (10.1 mm) in subject (b) (6), an 81-year-old male with Alzheimer's disease dementia who received a single dose of study drug at 1 mg/kg in Study 104 for which she could not identify a clear non-drug etiology; events of intracerebral hemorrhage greater than 1 cm in Subject (b) (6) on lecanemab 10 mg/kg biweekly in 201 Core and in Subject (b) (6) in 201 OLE; and an event of subdural hematoma in 1 patient on lecanemab 10 mg/kg biweekly in the setting of ARIA-E and -H in 201 Core. This is in comparison to 3 subjects with intracranial hemorrhage on placebo with no clear etiology and no associated ARIA. In addition, there was a death in subject (b) (6) in 301 core due to intracranial hemorrhage with no report of ARIA, with reported concomitant medication of acetylsalicylic acid 81 mg daily; the patient was taking placebo. Advanced age and male sex are risk factors for intracranial hemorrhage and any potential role for lecanemab in these cases is not clear.

Dr. Erten-Lyons shows that most TEAEs in 201 Core were mild or moderate in severity based on impact on normal daily activity; that was true across all dose groups as well as in 201 OLE. Approximately 10% of subjects in the lecanemab 10 mg/kg biweekly group in 201 Core and approximately 3% in the 201 OLE study had a severe TEAE. The most frequent severe TEAEs (incapacitating, with inability to work or perform normal daily activity) in the lecanemab 10 mg/kg biweekly group in 201 Core were ARIA-E that occurred in 3 patients (2% in lecanemab 10 mg/kg biweekly vs. 0% on placebo), cerebral microhemorrhage (ARIA-H) that occurred in 2 patients (1% in lecanemab 10 mg/kg biweekly vs. 0% on placebo), and headache that occurred in 2 patients (1% in lecanemab 10 mg/kg biweekly vs. 0 on 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 used to manage treatment with lecanemab.

Discontinuations Due to Adverse Events

In Study 201 Core, 54% of patients in the lecanemab 10 mg/kg biweekly group (and 61-72% in other dose groups) completed study compared to 72% of patients on placebo. Thirty-three percent (25/74) who discontinued the study in the lecanemab 10 mg/kg biweekly group discontinued because of a change in protocol for those with ApoE ε4 carrier status. Adverse events leading to study withdrawal occurred in approximately 8% of patients on lecanemab 10 mg/kg biweekly compared to 4% on placebo. Treatment discontinuation occurred in approximately 15% (24/161) of patients on LEC-10 BW vs. approximately 6% (14/245) on placebo. Treatment discontinuation because of adverse events in lecanemab 10 mg/kg biweekly was driven by per protocol discontinuation for ARIA, with 16 patients (10%) discontinuing because of ARIA-E, 1 patient (0.6%) because of superficial siderosis, and 2 patients (1.2%) because of ARIA-H cerebral microhemorrhage in 201 Core. Discontinuation of study treatment due to adverse reactions other than ARIA-E occurred in 5.0% (8/161) of patients treated with lecanemab 10 mg/kg biweekly compared to 5.3% (13/245) of placebo treated patients. In the 201 OLE, 9/180 (5%) patients discontinued due to adverse events, 2 TEAEs of which occurred beyond 30 days of the last dose of study drug, and none of which occurred in more than 1 patient.

Treatment-Emergent Adverse Events (TEAEs) of All Severities

There was no imbalance in the incidence of TEAES overall in the lecanemab 10 mg/kg biweekly group compared to placebo. As Dr. Erten-Lyons notes, because of the risk of ARIA-E in ApoE ε4 carriers, that randomization of ApoE ε4 carriers to the lecanemab 10 mg/kg biweekly group was halted with only 30% of subjects in that group being carriers compared to 71% in the placebo group and compared to approximately 30-70% in the general population in patients with Alzheimer's disease. In addition, exposure to study drug in ApoE ε4 carriers was shorter in ApoE ε4 homozygotes (average of 247 days) vs. noncarriers (7015 days). Therefore, as Dr. Erten-Lyons suggests, the TEAEs observed in 201 Core at the proposed dose may not accurately represent what may be observed in the general

population of patients with Alzheimer's disease. The most frequently reported TEAEs in 201 Core at the lecanemab 10 mg/kg biweekly dose were infusion related reaction, ARIA-E, headache, and cough (see Table 4). Dr. Erten-Lyons also performed the TEAE analysis in patients without ARIA and shows that that most of the TEAEs occurred with similar incidence as observed in the full analysis, suggesting that most of the TEAEs are not related to ARIA.

Table 4 TEAEs by Preferred Term with an incidence at least 5% in the proposed dose arm and at least 2% greater than placebo in 201 Core

Dictionary Derived Term	Lecanemab 2.5 mg/kg biweekly N=52 N (%)	Lecanemab 5 mg/kg monthly N=51 N (%)	Lecanemab 5 mg/kg biweekly N=92 N (%)	Lecanemab 10 mg/kg monthly N=253 N (%)	Lecanemab 10 mg/kg biweekly N =161 N (%)	Placebo N= 245 N (%)
Infusion related reaction	3 (6)	4 (8)	11 (12)	59 (23)	32 (20)	8 (3)
Amyloid related imaging abnormality-oedema/effusion	1 (2)	1 (2)	3 (3)	25 (10)	16 (10)	2 (1)
Headache	8 (15)	4 (8)	17 (19)	41 (16)	22 (14)	25 (10)
Cough	1 (2)	2 (4)	4 (4)	11 (4)	14 (9)	12 (5)
Diarrhea	5 (10)	7 (14)	12 (13)	16 (6)	13 (8)	12 (5)
Cerebral microhemorrhage (ARIA-H)	2 (4)	7(14)	10 (11)	18	9 (6)	11 (4)

This table was created using the ISS ADAE dataset, Study identifier= BAN2401-G000-201, safety population flag= yes, treatment emergent flag = yes, grouped on USUBJID, Dictionary derived term, and actual treatment for period 01, then tabulated by Actual treatment for period 01 and dictionary derived term

Dr. Erten-Lyons presents in her review FDA grouped terms that were reported with an incidence of at least 2% and at least 2% greater than placebo in 201 Core. 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 TEAEs identified above, the grouped analysis shows a greater incidence in lecanemab 10 mg/kg biweekly vs. placebo of Hemorrhage FDA N (19% vs. 16%), Irritability (5% vs. 2%), diabetes-related terms[5] (5% vs. 1%), and Viral infections (6% vs. 4%), as well as the following groupings that occurred in 5% or fewer in lecanemab 10 mg/kg biweekly: Supraventricular Tachycardia (driven by atrial fibrillation), Myalgia, Hematuria, and Bronchospasm. Hemorrhage was driven by cerebral microhemorrhage (ARIA-H), contusion, and hematuria; Viral infections were driven by influenza and herpes zoster. Hemorrhage FDA N excluding ARIA H (brainstem microhemorrhage, cerebellar

[5] Diabetes, glucose intolerance, hyperglycemia, HbA1c, glycosuria, ketones.

microhemorrhage, cerebral microhemorrhage) and excluding cerebral hemorrhage, occurred in 13% in lecanemab 10 mg/kg biweekly vs. 11% in placebo, with hematuria being the only term more than 2% greater than placebo (4% vs. 2%). In other groupings, the individual terms were generally small in number, related but distinct concepts (such as for irritability), or may have resulted from baseline differences in risk factors such as for diabetes-related terms. Of note, in evaluating urine analysis, Dr. Erten-Lyons did not find a difference in occult blood observed in urine in lecanemab 10 mg/kg biweekly vs. placebo in 201 Core. She also notes that in most cases of hematuria, there was another clear cause, except in 1 patient on lecanemab 5 mg/kg biweekly with 1 episode of hematuria for which she could not rule out a role of study drug, which resolved the next day, and for which no action was taken with study drug.

Dr. Erten-Lyons evaluated baseline demographics, medical history, and concomitant medications that could explain the increased incidence of cough and finds an increased prevalence of asthma and chronic obstructive pulmonary disease in the lecanemab 10 mg/kg biweekly arm compared to placebo.

In Study 201 OLE, the most common TEAEs included infusion related reactions (21%), fall (20%), urinary tract infection (14%), cerebral microhemorrhage (ARIA-H;12%), and nasopharyngitis (10%). Dr Erten-Lyons notes that the incidence of falls in 201 Core was not greater in lecanemab 10 mg/kg biweekly than in placebo, and that the incidence of falls in the 201 OLE is within the reported rate for adults over 65 years old in the general population.

Laboratory Findings

Hematology

Review of laboratory findings in 201 Core showed a dose-dependent decrease in lymphocytes and a dose-dependent increase in neutrophils and leukocytes after the first infusion in which blood samples were collected at 4 hours after the dose (Visit 3/Week1). A small transient decrease in platelet counts was also observed. The mean decrease in lymphocyte count in lecanemab 10 mg/kg biweekly was -0.7 x 109/L at that visit. The mean increases in neutrophil count and leukocyte count at that visit for lecanemab 10 mg/kg biweekly at that visit were 2 x 109/L and 1.1 109/L, respectively. Dr. Erten-Lyons points out that in subsequent assessments blood was collected prior to infusion so it is not known whether the observed changes occur after each infusion. However, although some individuals had several instances of such changes, the changes in lymphocytes, neutrophils, and leukocytes appeared to be transient and did not persist on average across the study visits. Across study visits in 201 Core, among patients with normal values at baseline, the overall incidence of low lymphocytes (below the lower limit of normal, LLN) was 42% for lecanemab 10 mg/kg biweekly vs. 9% for placebo and the incidence of high neutrophils (greater than the upper limit of normal, ULN) was 24% for lecanemab 10 mg/kg biweekly vs. 9% for placebo. Excluding the week 1 post-infusion time point, there was not an increased risk of these hematologic changes across the duration of the study. In the OLE, there was no post-infusion

laboratory assessment. Dr. Erten-Lyons notes no notable mean changes in hematologic parameters in the OLE, with up to 9% of patients having shift to low lymphocyte count at any time through week 39 of the OLE (compared to 1-3% of patients in the 201 Core. Markedly abnormal low lymphocytes (<0.8x109/L) occurred in 34% in the lecanemab 10 mg/kg biweekly arm vs. 5% in placebo. As Dr. Erten-Lyons notes, it is difficult to interpret these findings in the OLE without a comparator group. Dr. Erten-Lyons also notes a transient dose-dependent reduction in lymphocyte count and increase in neutrophil count associated with study drug administration in Phase 1 Study 101 (single ascending and multiple ascending dose study in patients with mild to moderate Alzheimer's disease).

Dr. Erten-Lyons identified 12 subjects in 201 Core across all doses with TEAEs of reduction in lymphocyte count/lymphopenia. She notes a dose-response for that finding and notes that 9/12 of the participants had a single episode of lymphocyte count below the lower limit of normal on Study Day 1 that normalized around Study Day 15 and did not recur with continued study drug administration. She also notes that in most of these subjects had elevated neutrophil counts on Study Day 1 as well. Dr. Erten-Lyons identified 4 subjects who had a TEAE of lymphopenia and an infusion-related reaction, 3 of whom had these findings on Study Day 1 after the first infusion, and 1 subject who had a TEAE of reduced lymphocyte count after the first dose and an infusion related reaction on Study Day 29 with ongoing reduced lymphocyte count. Dr. Erten-Lyons did not identify an increased risk of infections associated with the TEAE of lymphopenia or reduction in lymphocyte count. There is no evidence to suggest that the platelet abnormalities led to a higher risk of bleeding or that changes in hematology values led to other clinical adverse effects.

Dr. Erten-Lyons notes that on Day 1 (day of the first dose), among subjects with symptomatic infusion-related reactions, the incidence of high neutrophils was 31% and low lymphocytes was 69%. In response to an information request, the applicant provide citations to support that these hematologic changes have been observed with other monoclonal antibodies, although it is not clear in those publications if this was associated with an infusion-related reaction. As Dr. Erton-Lyons suggests, it is plausible that the change changes in lymphocytes observed right after the infusion may be related to a transient reaction to the infusion.

Chemistry

Dr. Erten-Lyons does not find a clear trend for persistently lower or higher chemistry values for lecanemab 10 mg/kg biweekly or other treatment arms compared with placebo, except for globulin low, protein low, and glucose high in which globulin low (61% in lecanemab 10 mg/kg biweekly vs. 48% for placebo), protein low (22% for lecanemab 10 mg/kg biweekly vs. 14% for placebo), and glucose high (8% for lecanemab 10 mg/kg biweekly vs. 5% for placebo) that occurred at any postbaseline visit. In the 201 OLE, there was a shift to abnormally low globulin in 45% and a shift to high for glucose in 25%. Sixteen percent had one or more low protein values at any postbaseline visit. In Study 201 Core there was an imbalance in markedly abnormal high glucose (fasting > 160) in 9% of patients in lecanemab 10 mg/kg biweekly vs. 5% in placebo, markedly abnormal high potassium (>5.5 mmol/dL) in 7% of

patients in lecanemab 10 mg/kg biweekly vs. 4% in placebo. As Dr. Erten-Lyons notes, the significance of these changes is not clear. As she previously noted, an imbalance was observed in the TEAE grouped query for diabetes with an incidence of 5% in the lecanemab 10 mg/kg biweekly arm vs. 1% in placebo in 201 Core. However, she also notes a baseline imbalance in the lecanemab 10 mg/kg biweekly arm compared to placebo in patients with Type 2 Diabetes (13 % % vs. 8 %) and obesity (3 % vs. 1 %) at baseline that could confound these chemistry and TEAE findings. Because of this uncertainty, the imbalance in diabetes-related findings will not be included in labeling until data from a larger database are available to provide clarity.

Dr. Erten Lyons does not find a signal for hepatoxicity in patients treated with lecanemab.

Urinalysis

Dr. Erten-Lyons finds an imbalance in urine glucose at the week 1 visit and at the 79-week visit (2 weeks after the last dose of study drug). In both cases this was reported in 6% in lecanemab 10 mg/kg biweekly vs. 2% in placebo, although the trend was not observed consistently at every visit. AS Dr. Erten-Lyons notes, the significance is unclear. However, this finding is consistent with the reported TEAEs of hyperglycemia and glycosuria.

Vital Signs

There were no clinically significant changes in vital sign parameters in patients treated with lecanemab.

After the first infusion at week 1, 1/160 (0.6%) patients on lecanemab 10 mg/kg biweekly had an elevated temperature, consistent with an infusion reaction, vs. none on placebo. Dr. Erten-Lyons notes a slight decrease in mean heart rate of 2 beats per minute post-infusion in lecanemab arms that was not observed in the placebo arm in 201 Core. Mean heart rates remained in the normal range. Similar frequencies of patients had shift from normal baseline heart rate to low heart rate (< 50 bpm) post-infusion for lecanemab 10 mg/kg biweekly (8%) vs. placebo (7%). Dr. Erten-Lyons also finds a dose dependent decline in the RR interval post-infusion for lecanemab vs. placebo in Study 104, consistent with the findings of slightly decreased post-infusion heart rate in 201 Core. Dr. Erten-Lyons does not identify any TEAEs in the lecanemab 10 mg/kg biweekly related to vital signs that were more than 2% than in placebo and did not find a higher incidence of TEAEs of bradycardia, hypotension, or syncope in the lecanemab 10 mg/kg biweekly arm compared to placebo. The TEAE of orthostatic hypotension was slightly higher in the proposed dose arm compared to placebo (1.8% vs. 0.4%). Findings in the 201 OLE were similar to those in the 201 Core Study. In Study 104, Dr. Erten-Lyons finds a higher incidence of low systolic blood pressure and low diastolic blood pressure in lecanemab arms vs. placebo in lecanemab 10 mg/kg biweekly vs. placebo; the numbers of patients with such measurements at any given time point are small.

ECG/QT

There were no clinically meaningful changes in ECG parameters in patients treated with lecanemab. In accordance with ICH E14 guidelines for monoclonal antibodies, a thorough QT study was not conducted.

Subgroup Analyses

In 201 Core, the incidence of ARIA-E, headache, and diarrhea were greater in women than in men, for both lecanemab 10 mg/kg biweekly and for placebo. The incidence of ARIA-E, headache, and diarrhea in the lecanemab 10 mg/kg biweekly -treated patients was greater in patients at least 65 to less than 80 years old than in younger or older age groups. Patients less than 65 years old had an increased incidence of cough, and Dr. Erten-Lyons does not find a clear underlying mechanism for this difference. Age-related findings are limited by the small number of patients in age groups of less than 65 (n=28) and 80 or older (n=34) compared with at least 65 to less than 80 years old (n=99). The numbers of patients 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.

Other Events of Interest

Amyloid-Relating Imaging Abnormalities (ARIA)

The following discussion refers to data from 201 Core unless otherwise indicated.

Table 5, extracted from Dr. Erten-Lyon's review shows the incidence of ARIA events, within 30 days of a dose of lecanemab, in 201 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 5 Number of participants with one or more Treatment Emergent ARIA Events in Study 201 Core flag as per applicant definition). [3]

	Lecanemab 2.5 mg/kg biweekly N=52 N (%)	Lecanemab 5 mg/kg monthly N=51 N (%)	Lecanemab 5 mg/kg biweekly N=92 N (%)	Lecanemab 10 mg/kg monthly N=253 N (%)	Lecanemab 10 mg/kg biweekly N =161 N (%)	Placebo N= 245 N (%)
ARIA	4 (8)	7 (14)	16 (17)	38 (15)	20 (12)	13 (5)
ARIA-E	**1 (2)**	**1 (2)**	**3 (3)**	**25 (10)**	**16 (10)**	**2 (1)**
ARIA-H	**3 (6)**	**7 (14)**	**13 (14)**	**25 (10)****	**10 (6)**	**12(5)**
Isolated ARIA-H	3 (6)	6 (12)	13 (14)	13 (5)	4 (2)	11 (4)
Superficial Siderosis	0	1(2)	3 (3)	6 (2)	1 (1)	1 (0.4)
ARIA-Microhemorrhage	3 (6)	7 (14)	11 (12)	19 (8) ***	9 (6)	11 (4)

** Participants with an incident ARIA-H event (whether treatment emergent or not) while a treatment emergent ARIA- E event was radiographically present was captured under co-occurrence of ARIA-E and ARIA-H*
*** Cerebellar microhemorrhage in these participants were included under ARIA-H microhemorrhage*
**** These numbers include participant* (b) (6) *who was identified to have an ARIA-H event by the applicant during a data reconciliation and alerted the FDA on August 12, 2022. Because of lack of additional information from the study site, the applicant did not include this event in the sequence 60 submitted ADAE dataset. But this participant is counted in the table above.*

As shown in Table 5, in the placebo-controlled study 201 Core, overall ARIA was observed in 12% of patients treated with lecanemab 10 mg/kg biweekly, compared to 5% of patients on placebo. ARIA-E was observed in 10% of patients on lecanemab 10 mg/kg biweekly compared to 1% of patients on placebo. ARIA-H was observed in 6% of patients on lecanemab 10 mg/kg biweekly compared to 5% of patients on placebo. In the 201 OLE, the incidence of ARIA-E in the 45 participants who received placebo during 201 Core and then received lecanemab 10 mg/kg biweekly in the OLE was 4/45 (9%), similar to the incidence observed in 201 Core. The incidence of ARIA-H in the OLE as 13% in all patients and 11% in the OLE patients who had been treated with placebo in 201 Core. Dr. Erten-Lyons hypothesizes that the longer duration of exposure, allowing participants to be on anticoagulants, and continued dosing after an ARIA event may have contributed to more ARIA-H events in the OLE.

In study 201 Core, intracerebral hemorrhage greater than 1 cm in diameter was reported in one patient on lecanemab and no patients on placebo. One event of intracerebral hemorrhage was reported in 201 OLE in a patient with cerebral amyloid angiopathy and taking aspirin 81 mg. Additional narratives of intracerebral hemorrhage from 301 Core were submitted to the BLA and are described in Dr. Erten-Lyons' review. There was one death due to intracerebral hemorrhage in 301 Core in a patient receiving placebo, and two deaths in 301 OLE that are described in the section on deaths above. It is reported in Study 301 Core

that intracerebral hemorrhage occurred in 5 of 898 participants (0.6%) in the lecanemab group and 1 of 897 participants (0.1%) in the placebo group; however, the Division is not able to confirm these results at this time.

The majority of ARIA cases in 201 Core were asymptomatic. Clinical symptoms were present in 5/20 of patients who had ARIA in the lecanemab 10 mg/kg biweekly dose group compared to 0/2 in placebo patients who had ARIA. Of the 5 patients with symptoms in the proposed dose arm, 4 were ApoE ε4 homozygotes and 1 was a noncarrier. The most common symptom in patients with ARIA at the proposed dose was headache that occurred in 3/5 patients. Agitation, confusional state/mental status, and vision blurred each occurred in 2 patients. One possible seizure was reported but could not be confirmed. Other AEs that occurred in 1 patient each were burning sensation/paraesthesia, visual field defect/homonymous hemianopia, affect lability, aphasia, clonus, confabulation, abnormal ECG, hallucination, hyperreflexia, and vomiting. The symptoms were reported as serious in patients with ARIA treated with lecanemab 10 mg/kg biweekly.

In the 201 OLE, 3/14 (21%) of patients with ARIA had clinical symptoms; these included headache and dizziness, none of which was serious. Dr. Erten-Lyons did not identify any deaths in studies, 101, 104, 004 and 201 Core or OLE phase due to ARIA.

Early during the 201 Core study, European regulators requested that ApoE ε4 carriers not be randomized to lecanemab 10 mg/kg biweekly because of a higher risk of ARIA-E, and ApoE ε4 carriers randomized to lecanemab 10 mg/kg biweekly and treated for a duration of less than 6 months were to be discontinued from the study. In 201 Core, 6% (10/161) of patients in the lecanemab 10 mg/kg biweekly group were ApoE ε4 homozygotes, 24% (39/161) were heterozygotes, and 70% (112/161) were noncarriers. In 201 Core, the incidence of ARIA-E was higher in ApoE ε4 homozygotes (5/10; 50%), than in heterozygotes (2/39; 5%) or in non-carriers (9/112; 8%) treated with lecanemab 10 mg/kg biweekly (7/49; 14% in carriers overall). Of the 5 ApoE ε4 homozygotes with ARIA in, 4 had symptomatic ARIA, 2 with severe symptoms. Similar findings were observed for ARIA-H microhemorrhage (3/10; 30%) in homozygotes, 3/39 (8%) in heterozygotes, and 3/112 (3%) in noncarriers. In 201 OLE in which enrollment of ApoE ε4 carriers was allowed throughout the study, the incidence of ARIA-E was greater in ApoE ε4 homozygotes (4/28; 14%) compared to heterozygotes (9/97; 9%) or noncarriers (1/55; 2%). ARIA-H microhemorrhage and superficial siderosis similarly occurred with a greater incidence in carriers than in noncarriers in the OLE. Although there are limitations to the interpretation of the analyses by ApoE ε4 carrier status due to the small numbers, unbalanced subgroups, and limited duration of exposure in carriers, similar findings have been reported in Study 301 Core. As ApoE ε4 patients have a higher incidence of ARIA, including symptomatic ARIA, testing for ApoE ε4 status should be considered to inform the risk of developing ARIA when deciding to initiate treatment with lecanemab.

Among the 16 patients treated with lecanemab 10 mg/kg biweekly who had ARIA-E in 201 Core, the maximum radiographic severity was mild in 7 (44%), moderate in 7 (44%), and

severe in 2 patients (12%). In most patients ARIA-H was mild; ARIA-H microhemorrhage was severe in 2 patients (1%).

Routine Safety MRIs to monitor for ARIA were to be performed to prior to the 5th, 7th, 14th, 20th, 27th, and 33rd infusions and 2 weeks after the last dose.

Table 6, extracted from Dr. Erten-Lyons' review, shows the timing of first ARIA-E events in the lecanemab 10 mg/kg biweekly group in study 201 Core.

Table 6 Timing of first ARIAE events in Lecanemab 10 mg/kg Biweekly group in study 201 Core

Number of doses received prior to ARIA-E	# of Patients experiencing a first ARIA-E	Cumulative frequency of first ARIA-E N (%)
3	1	1 (6)
4	2	3 (19)
5	1	4 (25)
6	8	12 (75)
11	1	13 (81)
26	1	15(94)
32	2	16 (100)

The majority of ARIA-E radiographic events occurred by the 11th dose. Of patients with ARIA-E, approximately 6% of had a first episode of ARIA-E prior to the 4th dose, and cumulatively 19% prior to the 5th dose, cumulatively 25% prior to the 6th dose, and cumulatively, 75% prior to the 11th dose; Beyond that period, additional first episodes of ARIA occurred in 1/16 patients between the 11th and 12th doses, 1/16 occurred between the 26th and 27th doses, and 2/16 between the 32nd and 33rd doses. Similarly, in the OLE, 79% of cases had occurred by the 12th dose. In the OLE, one patient had multiple events of ARIA-E, 3 of which occurred after the 24th dose. Dr. Erten-Lyons notes that in 201 Core, 2 subjects in the lecanemab 10 mg/kg monthly arm who had a treatment-emergent ARIA-E event leading to study drug discontinuation had an additional ARIA -E event at 113 days and 169 days, respectively, after the last dose. One subject in the lecanemab 10 mg/kg monthly arm who had a treatment emergent ARIA-H microhemorrhage, but not a treatment emergent ARIA-E event, had an ARIA-E event 136 days after the last dose. Events of ARIA-H (including in 6 lecanemab 10 mg/kg biweekly patients (4%)) had ARIA -H microhemorrhage beyond 30 days after the last dose. The relationship to study drug is unknown; cerebral microhemorrhage as well as ARIA-E can in absence of lecanemab.

After detection, resolution of ARIA-E was reported in 15/16 (94%) of patients, resolving on average in 89 days (37-258 days). Resolution occurred in approximately 62% of ARIA-E

patients by 12 weeks, 79% by 21 weeks, and in approximately 96% overall after detection. In 201 OLE, ARIA-E resolved in 14/14 patients, on average in 107 days (range 29-368 days). In 201 Core, participants who had ARIA-E of any radiographic severity were discontinued from study drug. In 201 OLE, patients could continue to participate in the study with the following limitations:

- Asymptomatic ARIA-H (fewer than 10) cerebral microhemorrhages – no study drug action required
- Symptomatic ARIA H – drug administration temporarily stopped until ARIA-H stabilizes radiographically and is no longer symptomatic. Resumption following symptomatic ARIA-H can only occur twice, after which the subject would be discontinued form the study.
- More than 10 symptomatic cerebral microhemorrhages, superficial siderosis, or a single macrohemorrhage greater than 10 mm – additional safety visits with MRI until asymptomatic ARIA-H stabilizes radiographically.
- Radiographically mild or moderate asymptomatic ARIA-E – continue study drug unless it becomes radiographically severe or participant becomes symptomatic.
- Symptomatic or radiographically severe ARIA-E – drug administration temporarily stopped until ARIA-E resolves radiographically. Resumption of treatment could only occur twice, after which the subject would be discontinued from the study.

In 201 Core, subjects with ARIA were to be discontinued from study drug. However, 5 patients continued to be dosed through the event. None had further ARIA events, although 1 had radiographic worsening. Among the 14 patients with ARIA-E in the OLE, 7 either continued dosing or had dosing interrupted, none of whom developed further ARIA-E events. The other 7 patients had worsening of ARIA E (in 5 patients) or at least 1 additional event of ARIA-E (in 3 patients). As Dr. Erten-Lyons notes, whether an event of ARIA predicts the occurrence of future events is not known. There is no experience in the OLE with continued dosing through symptomatic, radiographically mild ARIA-E.

In 201 Core, ARIA-H in the setting of ARIA-E associated with the use of lecanemab 10 mg/kg biweekly was observed in 4% compared to 1 of patients on placebo. There was no imbalance in isolated ARIA-H. Cerebral hemorrhage greater than 1 cm was reported in 1 patient on lecanemab 10 mg/kg biweekly and in no patients on placebo.

Dr. Erten-Lyons notes that the protocol for 201 Core, did not permit use of anticoagulants other than short term (4 weeks) of treatment for randomized subjects who underwent procedures requiring anticoagulants for prophylaxis, during which time study drug was temporarily suspended. The protocols 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), uncontrolled hypertension with a history of blood pressure consistently above 165/100 mm Hg at screening, and evidence of multiple lacunar infarcts or stroke involving a major vascular territory. In patients treated with lecanemab 10 mg/kg biweekly, Dr. Erten-Lyons shows that patients who received antithrombotic

medication preceding an ARIA-H event had a slightly higher incidence of ARIA -H microhemorrhage or superficial siderosis (5/85; 6%) than in patients who had no-anti-thrombotic use (3/76; 4%); similar findings were observed in placebo patients (5% on antithrombotics vs. 4% not on antithrombotics). The majority of exposures to antithrombotic medications were to aspirin (91%). Dr. Erten-Lyons notes that in the OLE, ARIA-H occurred in 17% of patients on antithrombotic vs. 9% in patients not on antithrombotic. Patients in the OLE who were ApoEe4 carriers were allowed to participate and if ARIA-H or cerebral hemorrhage were asymptomatic the patient could continue treatment. It is possible that those differences could account for an increased observation of ARIA H in either group of patients in the OLE than was observed in 201 Core, although it is difficult to determine in the absence of a placebo group. The small numbers of exposures to antithrombotic medications in general, and non-aspirin medications in particular, and the small numbers of patients with ARIA, do not allow for meaningful conclusions about an increased risk of ARIA-H or intracerebral hemorrhage for lecanemab with concurrent antithrombotic use. However, because intracerebral hemorrhages greater than 1 cm in diameter have been observed in patients taking lecanemab, labeling will recommend 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.

Because risk factors for and clinical presentation of ARIA appears to be similar across anti-amyloid monoclonal antibody products, a similar approach to management of ARIA for different anti-amyloid monoclonal antibody products is reasonable based on the currently available data. 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.

Recommendations for dosing interruptions for ARIA events that will be described in labeling are shown in Table 7 and Table 8.

Table 7: Dosing Recommendations for Patients 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 8: Dosing Recommendations for Patients 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; 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.

Dr. Erten-Lyons notes in her review that there is insufficient data in the current submission regarding the continuation of dosing with lecanemab in patients with mild symptoms associated with mild radiographic ARIA-E. The recommendation to continue dosing is consistent with the aducanumab label. The rationale for this recommendation 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. Therefore, it was determined that prescribers should use in clinical judgment in determining if the presence of mild symptoms are of clinical concern and should preclude continued dosing.

In patients who develop intracerebral hemorrhage greater than 1 cm in diameter during treatment with lecanemab, it is recommended that dosing with lecanemab be suspended until an MRI demonstrates radiographic stabilization and symptoms, if present, resolve. 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.

Safety MRI monitoring in Core 201 was performed before the 5th, 7th, 14th, 20th, 27th, 32nd, and 40th doses. As noted above, the majority of ARIA occurred between the 4th and

12th doses (week 23) at which point 81% of the first events of ARIA had occurred (with 94% occurring before the 27th dose at week (53). The Applicant proposes enhanced clinical vigilance during the first 14 weeks of treatment with lecanemab, and proposes MRIs between the (b) (4) with additional MRIs if clinically indicated.

Dr. Erten-Lyons proposes safety MRIs prior to the 5th, 7th, and 14th infusions, with continued clinical monitoring during the course of treatment and up to 6 months after treatment, with unscheduled MRIs for emerging clinical symptoms suggestive of ARIA. This proposal is reasonable, although only 1 ARIA event occurred between the 6th and 11th doses, and then the additional cases did not occur until after the 25th dose. It is not known whether more frequent MRI monitoring impacts clinical outcomes from ARIA. However, Dr. Erten-Lyons' proposed schedule, consistent with that performed in Study 201, would be reasonable to recommend until more data become available to inform optimal monitoring for ARIA with lecanemab. Recommendations for extended MRI monitoring should take into consideration the uncertainty regarding drug-relatedness of these events, the uncertainty in the benefit of frequent monitoring by MRI, particularly in this period, and acknowledging the burden to patients of additional MRI monitoring in the absence of ARIA-related symptoms.

Infusion Reactions

In 201 Core there was a dose-dependent increased incidence of infusion related reactions in patients receiving lecanemab vs. placebo. Thirty-two of 161 (20%) lecanemab 10 mg/kg biweekly subjects vs. 8 (3%) subjects on placebo had at least 1 infusion related reaction. The maximum severity was mild in 56% of lecanemab 10 mg/kg biweekly subjects and moderate in 44%. One subject in 201 Core had an infusion reaction categorized as a SAE after administration of lecanemab 10 mg/kg biweekly (described below). At the proposed dose, the infusion reaction occurred at the time of the first infusion in 28/32 (88%) patients. There were no participants who had infusion interrupted due to an infusion-related reaction in the lecanemab 10 mg/kg biweekly group, although 1 subject in the lecanemab 5 mg/kg biweekly group and 2 in the lecanemab 10 mg/kg monthly had an infusion interruption due to such a reaction. Four of 161 subjects (2%) in the lecanemab 10 mg/kg biweekly group vs. 2 /245 (1%) in the placebo group had study drug discontinued due to an infusion related reaction.

Some patients who had an infusion reaction received preventive medications such as ibuprofen, paracetamol, and diphenhydramine with subsequent infusions. Dr. Erten-Lyons notes that 20/27 (74%) who had subsequent infusions did not have a subsequent infusion related reaction, although 6 patients had subsequent infusion reactions despite pre-medication. Infusion related reactions were treated with nonsteroidal anti-inflammatory drugs, analgesics/antipyretics, antiemetics, antihistamines, or corticosteroids.

Symptoms commonly described were fever and flu-like symptoms (chills, generalized aches, feeling shaky, and joint pain). Some participants experienced hypotension, hypertension, nausea, vomiting, or desaturation. One patient had a rash occurring right after the infusion.

Shortness of breath, slight tremors, uncontrollable shaking, and headache were also reported. No patient experienced an anaphylactic reaction. One patient had a SAE of infusion reaction in lecanemab 10 mg/kg biweekly in 201 Core, with a reaction including dizziness, vomiting, chills, fever (38.5°C) during the 3rd hour post-infusion after the 2nd infusion, resulting in hospitalization and treated with dexchlorpheniramine, IV fluids, methylprednisolone, ondansetron, dexketoprofen, and pantoprazole. A SAE of an infusion - related reaction was reported in the 201 OLE in a patient after the 1st dose of lecanemab 10 mg/kg biweekly in the OLE (on placebo in 201 Core), with nausea, vomiting, agitation/confusion, and fever up to 38.8°C), and lab results showing elevated C-reactive protein, and including low lymphocytes and increased neutrophils.

Hypersensitivity Reactions

In 201 Core, hypersensitivity reactions, excluding infusion reactions, occurred in 12/161 (7%) patients in the lecanemab 10 mg/kg biweekly group vs. 23/245 (9%) in the placebo group. There was not a dose response across lecanemab doses. In the lecanemab 10 mg/kg biweekly group, hypersensitivity reactions reported were drug eruption, eczema, macular rash, hypersensitivity, allergic sinusitis, and multiple allergies that each occurred in 1% vs. none in placebo. Among the hypersensitivity terms, only skin reaction terms (drug eruption and various rash terms) were greater across all lecanemab (4%) groups vs. placebo (2%). Overall, there was no imbalance in the incidence of preferred terms related to skin reaction in lecanemab 10 mg/kg biweekly (2%) vs. placebo (2%), eyelid edema (mild in severity and nonserious) was reported in 1 subject in the lecanemab 10 mg/kg monthly group; the event resolved, and the patient continued dosing through the remainder of the study without further eyelid edema events. Most hypersensitivity reactions were mild and nonserious and resolved without intervention. In approximately 75% of subjects with a hypersensitivity reaction (excluding infusion reactions), onset was within 12 days of their most recent dose. In all lecanemab dose arms, 66% of skin reactions were mild, and none were serious or severe. In 90%, dosing was continued. One participant discontinued due to a drug eruption.

Suicidal behavior/ideation

There is not a signal for suicide-related events in Study 201 Core or OLE. A role for lecanemab in suicide-related events that occurred in completed studies or in blinded Study 301 cannot be determined.

Abuse Potential

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

Immunogenicity

Dr. Erten-Lyons notes that treatment emergent anti-lecanemab antibodies (ADA) were reported in at least 1 sample in approximately 41% (63/154) patients treated with

lecanemab 10 mg/kg biweekly and according to Dr. Yifei Zhang's Clinical Pharmacology review, these were generally characterized by low titers. Of these patients, treatment emergent anti-lecanemab neutralizing antibodies (Nab) were positive in at least 1 sample in 25% (16/63). However, Dr. Zhang notes that the plasma concentrations of lecanemab exceed 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. Dr. Zhang's review notes that this may result in an underestimation of ADA and Nab positivity. The assay limitations preclude definitive conclusions regarding the impact of ADA on lecanemab safety.

Carcinogenicity

An imbalance in the incidence of neoplasms was not identified between lecanemab and placebo. However, the mean duration of exposure of 52 weeks in the 201 Core study does not allow for conclusions regarding 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 approval of lecanemab for the proposed indication.

ARIA and infusion reactions will be described in the Warnings and Precautions section of the labeling. 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. Symptoms as well as possible preventive measures are provided for in section 5.1 and in the medication guide. The Agency will request enhanced pharmacovigilance focusing on the safety aspects of ARIA, including the risk of the use of thrombolytic therapy and further characterization of infusion reactions.

The Division of Risk Management has concluded 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 can be communicated through Section 5: Warnings and Precautions. Labeling will convey the risk of ARIA 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. Post-marketing

requirements include a confirmatory study. Enhanced pharmacovigilance for ARIA will be requested.

On December 16, 2022, the applicant provided a summary of its educational plan for prescribers to identify patients appropriate for lecanemab treatment, to identify and manage infusion related reactions, and to educate prescribers regarding ARIA, as well as an educational program for patients and caregivers.

The Agency has become aware of the Alzheimer's Network for Treatment and Diagnostics (ALZ-NET), a provider-enrolled patient registry that collects information on outcomes of treatments for Alzheimer's disease. This will be included in labeling advising prescribers to encourage patients to enroll.

8. Advisory Committee

The application did not raise new or unexpected safety or efficacy issues for a drug of this class.

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, number of subjects with amyloid PET scan data, and history of prior inspections. The review concludes that Study 201 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 from the Division of Risk Management for further details of this assessment.

Postmarketing Requirements (PMRs) and Commitments (PMCs)
The following PMRs will be issued:

- In order to verify the clinical benefit of lecanemab, conduct a randomized, controlled trial to evaluate the efficacy of lecanemab 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.

- Improve the sensitivity for the current anti-drug antibody (ADA) assay to at least 100 ng/ml in the presence of the trough level of drug expected to be present during sampling. If sensitivity for the current ADA assay cannot be improved, develop and validate an alternative assay with this level of sensitivity. Improve the sensitivity and drug tolerance for the current neutralizing antibody (NAb) assay. If sensitivity and drug tolerance for the current NAb assay cannot be improved, develop and validate an alternative assay with adequate sensitivity and drug tolerance. Include in the assay validation a statistical evaluation of distribution and outlier exclusion for cutpoint samples, selectivity, system suitability specifications for negative and positive controls, and effects of hemolysis. Refer to the 2019 FDA guidance for immunogenicity assays (https://www.fda.gov/regulatory-information/search-fda-guidance-documents/immunogenicity-testing-therapeutic-protein-products-developing-and-validating-assays-anti-drug), as this document recommends sensitivity in the range of 100 ng/ml or lower.

- Using the improved and validated assays developed in response to PMR#2, evaluate the impact of ADA and NAb on the pharmacokinetics, pharmacodynamics, safety, and efficacy of lecanemab in patients enrolled in the confirmatory study.

The following PMC will be issued:

Perform a shipping study to confirm validation of the commercial lecanemab drug product shipping conditions and provide the results of your study. The study will include monitoring of temperature during the shipment, testing of pre- and post-shipping samples for product quality (purity by SEC, cSDS reduced and non-reduced, IE-HPLC, sub-visible particles, and

potency of lecanemab), and confirmation that the commercial shipping configuration minimizes physical damage to drug product containers.

13. Comments to the Applicant

The following request for enhanced pharmacovigilance will be conveyed in the approval letter:

We request expedited reporting of any deaths in ongoing studies and of deaths resulting from cerebral hemorrhage greater than 1 cm in size 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 the registry
- Age
- Alzheimer's disease stage
- Patient characteristics, including APOε4 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 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.

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
01/06/2023 11:15:03 AM

SALLY U YASUDA
01/06/2023 11:17:00 AM

TERESA J BURACCHIO
01/06/2023 11:18:46 AM

TERESA J BURACCHIO on behalf of WILLIAM H Dunn
01/06/2023 12:23:09 PM