CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761248Orig1s000

SUMMARY REVIEW

Summary Memorandum

Date	July 2, 2024
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Subject	Summary Memorandum
BLA #	761248
Applicant	Eli Lilly and Company
Date of Submission	June 12, 2023
PDUFA Goal Date	March 12, 2024
Proprietary Name	Kisunla
Established or Proper Name	donanemab
Dosage Form(s)	Injection
Applicant Proposed Indication(s)/Population(s)	For the treatment of patients with Alzheimer's disease
Applicant Proposed Dosing Regimen(s)	700 mg administered as an intravenous infusion over approximately 30 minutes every four weeks for the first three doses, followed by 1400 mg every four weeks
Recommendation on Regulatory Action	Traditional Approval
Recommended Indication(s)/Population(s) (if applicable)	For the treatment of Alzheimer's disease

1. Benefit-Risk Assessment

Benefit-Risk Assessment Framework

Benefit-Risk Integrated Assessment

Alzheimer's disease (AD) is a neurodegenerative disease that causes progressive impairments in memory, language, and thinking, with the eventual loss of ability to perform social and functional activities in daily life. In general, the average survival is 4 to 8 years after a diagnosis of dementia due to AD. It is estimated that 6.7 million Americans age 65 and older are currently living with AD dementia, and AD is a leading cause of death in the United States. Acetylcholinesterase inhibitors (donepezil, galantamine, and rivastigmine) and the N-methyl-D-aspartate receptor antagonist memantine are approved therapies for the treatment of Alzheimer's disease, but they do not target the underlying pathology of the disease and their effects are modest and short-lived. Aducanumab and lecanemab are amyloid-beta directed antibodies that received accelerated approval and traditional approval, respectively, and are indicated for the treatment of Alzheimer's disease, specifically in patients with mild cognitive impairment (MCI) or mild dementia stage of disease. There is an urgent and unmet medical need for effective treatments for AD, and a particular unmet need for therapies in AD that slow, halt, reverse, prevent, or cure the disease, with an important focus on the development on drugs that target the underlying pathophysiology of AD in an effort to fundamentally affect the course of the disease.

Donanemab is an anti-amyloid beta (Aβ) monoclonal antibody targeting N-truncated pyroglutamate amyloid beta at position 3, which is present in brain amyloid plaques. 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 traditional approval based primarily on results from Study AACI, a multicenter, randomized, double-blind, placebo-controlled, parallel group study in subjects with early symptomatic Alzheimer's disease. Subjects were required to have evidence of brain amyloid and tau pathology on PET scans. The study included a screening period of up to 7 weeks, a 76-week placebo-controlled treatment period, and an immunogenicity and safety follow-up period of 44 weeks. Subjects were randomized to placebo or donanemab treatment in a 1:1 ratio in the placebo-controlled period. The primary efficacy endpoint was change in the integrated Alzheimer's Disease Rating Scale (iADRS) score from baseline to 76 weeks. Secondary endpoints

included change from baseline in the Clinical Dementia Rating Scale – Sum of Boxes (CDR-SB) and change from baseline of the two components of the iADRS: the Alzheimer's Disease Assessment Scale – Cognitive Subscale (ADAS-Cog 13) and the Alzheimer's Disease Cooperative Study – instrumental Activities of Daily Living subscale (ADCS-iADL) at week 76. There were two primary analysis populations based on visual and quantitative assessment of a tau PET scan: low/medium tau population and combined population of low/medium tau and high tau levels.

The primary efficacy endpoint analysis, change from baseline in iADRS at Week 76, demonstrated a statistically significant treatment effect in the donanemab treatment arm compared to placebo in both the combined tau population (2.92, $p<0.001$) and the low/medium tau population (3.25, $p<0.001$). Statistically significant reduction in clinical decline in the Division's recommended endpoint, CDR-SB, was also demonstrated, with a treatment effect of -0.70 [-29%], $p<0.001$ in the combined population. Nominal statistical significance was reached by Week 12 and was maintained through Week 76. Results were robust across sensitivity analyses. Statistically significant results favoring donanemab were observed for the multiplicity-controlled secondary endpoints ADAS-Cog 13 (-1.33 [-20%], $p<0.001$) and ADCS-iADL (1.70 [-28%], $p<0.001$) that are components of the iADRS. Donanemab treatment also demonstrated a statistically significant treatment effect on change from baseline in brain amyloid as measured by PET and reported as Centiloids at Week 76 (-86.4, $p<0.0001$). The robust, compelling, and consistent results across multiple clinical outcomes and biomarkers, and across multiple subgroups of the population, provide strong evidence for the effectiveness of donanemab for the treatment of Alzheimer's disease.

Overall, Study AACI is a large, multicenter, adequate and well-controlled study that demonstrated statistically persuasive and clinically meaningful benefits in cognition and function in subjects with Alzheimer's disease. The effect on the ADAS-cog, iADL, and CDR-SB endpoints in Study AACI represent a clinically meaningful reduction of clinical decline. The treatment effect is supported by the consistently favorable results across subgroups of interest defined by demographic and baseline disease characteristics. The effects on biomarkers reflecting brain amyloid plaque load and astrocytic activation support the observations on the clinical endpoints.

Study AACG is a smaller adequate and well-controlled Phase 2 study which achieved statistical significance on the primary endpoint (iADRS). Despite not reaching statistical significance according to the prespecified hierarchy, the estimates of the treatment effect at Week 76 across secondary endpoints are consistent in magnitude with the reduction of clinical decline on the same endpoints observed in Study AACI. Study AACG therefore contributes to the evidence for the effectiveness of donanemab.

Together, the results of these two adequate and well-controlled studies, AACI and AACG, provide substantial evidence of effectiveness for donanemab for the treatment of Alzheimer's disease. Although tau PET was used as an enrichment strategy in

the clinical studies, the data support the efficacy of donanemab across the range of levels on tau PET. The dosing regimens used in Study AACI and Study AACG ceased dosing based on threshold levels of amyloid on PET imaging. Although this approach is reasonable, it may be difficult to monitor amyloid by PET in clinical practice. Therefore, labeling will state that cessation of dosing may be considered based on amyloid reduction on PET imaging, but this will not be required. Given the uncertainty of long-term consequences after discontinuation of dosing when the amyloid threshold is reached, a postmarketing commitment will be issued to address the potential need for maintenance dosing.

The safety of donanemab was characterized in a safety database of adequate size. Study AACI provided the primary safety database for calculation of incidence rates, but safety data from AACG was also reviewed.

Monoclonal antibodies directed against aggregated forms of beta amyloid, such as donanemab, 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. Imaging findings of ARIA can also occur spontaneously in patients with AD or with cerebral amyloid angiopathy (CAA).

The most common adverse drug reactions with donanemab are ARIA-H microhemorrhage, ARIA-E, ARIA-H superficial siderosis, and headache. All occurred in at least 10% of subjects on donanemab and at least 2% more frequently than placebo in the controlled period of AACI.

There was an imbalance in deaths occurring within the 76 week placebo controlled on-study period in the donanemab-treated subjects (2.2%, 17/853) compared to placebo (1.2% (10/874), risk difference (95% CI) 0.6% (-0.6%, 1.8%) in Study AACI[1].

- 3 deaths were associated with ARIA in donanemab treated subjects compared to none on placebo
- 1 of those deaths was caused by intracerebral hemorrhage in the setting of ARIA-H in a patient with superficial siderosis at baseline compared to none in placebo
- In the all-donanemab pool, there was an additional death associated with ARIA and an additional death associated with intracerebral hemorrhage that occurred in a patient with ARIA-E, with symptoms mimicking stroke, who was treated with thrombolytic therapy.
- There was no other unusual cluster of deaths in the database.

[1] Calculated using Kaplan-Meier estimates of cumulative incidence

ARIA was observed in 36% (307/853) of subjects treated with donanemab, compared to 14 % (122/874) of subjects on placebo in AACI. Symptomatic ARIA occurred in 6% (52/853) of subjects treated with donanemab compared to none on placebo in AACI. The most common symptoms were headache and confusional state; other reported symptoms included dizziness, nausea, seizure, fatigue, gait disturbance, and tremor, consistent with symptoms reported for this class of drugs.

ARIA-E was observed in 24% (201/853) of subjects treated with donanemab compared to 2% (17/874) of subjects on placebo in AACI. Among the 853 subjects treated with donanemab, the maximum radiographic severity for ARIA-E was mild in 7%, moderate in 15%, and severe in 2%. The majority of ARIA-E radiographic events occurred early in treatment (within the first 7 doses). After detection, resolution occurred in 63 % of ARIA-E subjects by 12 weeks, 80% by 20 weeks, and in 83% by the end of the study overall.

ARIA-H was observed in 31% (263/853) of subjects on donanemab compared to 13% (111/874) of subjects on placebo in AACI. There was no imbalance in isolated ARIA-H for donanemab compared to placebo.

In AACI, 17% (143/850) of patients in the donanemab arm were apolipoprotein E ε4 (ApoE ε4) homozygotes, 53% (452/850) were heterozygotes, and 30% (255/850) were noncarriers, representative of the general population with AD. The incidence of ARIA in AACI was higher in ApoE ε4 homozygotes (55% on donanemab vs. 22% on placebo) than in heterozygotes (36% on donanemab vs 13% on placebo) and noncarriers (25% on donanemab vs 12% on placebo). Among subjects treated with donanemab, symptomatic ARIA-E occurred in 8% of ApoE ε4 homozygotes, compared with 7% of heterozygotes and 4% of noncarriers. Serious events of ARIA occurred in 3% of ApoE ε4 homozygotes, and approximately 2% of heterozygotes and 1% of noncarriers. Among subjects treated with donanemab who had ARIA E, severe radiographic ARIA-E was greatest in Apo E ε4 homozygotes (3%, 4/143) compared to heterozygotes (2%, 9/452) or noncarriers (0.4%, 1/255). Among subjects treated with donanemab who had ARIA-H, severe radiographic ARIA-H was greatest in Apo E ε4 homozygotes (22%, 31/143) compared to heterozygotes (8%, 38/452) or noncarriers (4%, 9/255).

Intracerebral hemorrhage greater than 1 cm in diameter was reported in 0.5% (4/853) subjects on donanemab and in 0.2% (2/874) subjects on placebo in AACI. Fatal events of intracerebral hemorrhage in subjects taking donanemab were reported in AACI and in the long-term extension (all donanemab pool) as noted above. The latter case was in the setting of symptoms of ARIA mimicking stroke, in which the subject was administered thrombolytic therapy in the absence of ischemic changes.

The incidence of ARIA-H in subjects who received donanemab and an antithrombotic medication was 30% compared to subjects who received no antithrombotic medication (29%). The incidence of intracerebral hemorrhage was 0.6% (2/349) in subjects taking donanemab with a concomitant antithrombotic medication at the time of the event compared to 0.4% (2/504 subjects) in those who did not receive an antithrombotic.

Hypersensitivity reactions, including angioedema and anaphylaxis occurred in subjects treated with donanemab in AACI. Infusion-related reactions occurred in 9% (74/853) of subjects on donanemab vs. 0.5% (4/874) in placebo-treated subjects in AACI. Infusion reactions were mostly mild (57%) or moderate (39%) in severity, and 70% occurred within the first 4 infusions. Symptoms associated with infusion reactions included chills, erythema, nausea/vomiting, dyspnea, sweating, elevated blood pressure (including 1 subject with a myocardial infraction within 5 minutes of starting the infusion), headache, chest pain, and low blood pressure. Sixty-eight percent (181/266) of subjects with an infusion reaction received subsequent infusions. Twenty-three percent (42/181) received preventative medication with subsequent infusions. The incidence of subsequent infusion-related reactions after a first event on donanemab was similar with (38%, 16/42) and without (41%, 57/139) preventative medication.

ARIA and infusion reactions are the primary risks associated with the use of donanemab. ARIA is usually asymptomatic. When symptomatic ARIA occurs, symptoms are usually mild or moderate, though serious asymptomatic (i.e., radiographic) and symptomatic cases can occur. The incidence of ARIA, including symptomatic ARIA, was higher in ApoE ε4 homozygotes compared to heterozygotes and noncarriers. Risk management for ARIA can be achieved through clear product labeling and monitoring for ARIA, as described in the label. A Boxed Warning will describe the overall risk of ARIA with donanemab treatment and will highlight the increased risk of ARIA, including symptomatic, serious, and severe radiographic ARIA, in ApoE ε4 homozygotes. The Boxed Warning will also describe fatal intracerebral hemorrhages that have occurred in subjects treated with donanemab, and will also caution physicians to consider whether focal neurologic symptoms could be due to ARIA-E when considering thrombolytic therapy in a patient taking donanemab. ARIA will also be further described in Section 5.1 Warnings and Precautions. The label will state that testing for ApoE ε4 status should be performed prior to initiation of treatment with donanemab to inform the risk of developing ARIA. Labeling will advise patients to carry information identifying them as users of donanemab and noting that symptoms of ARIA may mimic those of ischemic stroke. Postmarketing requirements (PMRs) will be imposed to further characterize risk factors for adverse outcomes associated with ARIA. A postmarketing commitment (PMC) will be agreed upon for development of a test for Apo E ε4 genotype. Enhanced pharmacovigilance will be performed to more fully characterize ARIA in the practice setting. Infusion-related reactions occurring in the controlled trial were moderate or mild, primarily occurring with first dose, and subsequently prevented in some cases by pre-treatment. Infusion reactions will receive a warning in labeling. Angioedema and anaphylaxis have occurred; there will be a contraindication for use in patients who have had a serious hypersensitivity reaction to donanemab. There are no safety issues that preclude approval.

Overall, the benefit-risk assessment is favorable and supports the approval of donanemab for the treatment of Alzheimer's disease, initiated in the mild cognitive impairment and mild dementia stages of the disease.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Alzheimer's disease is a progressive, degenerative brain disorder that affects memory, thinking, and behavior and is the most common cause of dementia. • Clinical symptoms include difficulty remembering recent conversations, names or events, impaired communication, disorientation, confusion, poor judgment, behavioral changes, and ultimately, difficulty walking, speaking, and swallowing. • Alzheimer's disease exists on a continuum from biological changes in the brain, to subtle problems with memory and thinking, and ultimately difficulties that affect an individual's ability to perform everyday activities. The disease process may begin 20 years or more before symptoms arise. • After a diagnosis of Alzheimer's dementia, the average survival is 4 to 8 years. • An estimated 6.7 million Americans age 65 and older are currently living with Alzheimer's disease. • Alzheimer's disease is a leading cause of death in the United States. • Almost two-thirds of Americans with Alzheimer's disease are women. Older African Americans and Latinos are disproportionately more likely to have Alzheimer's disease than White Americans.	Alzheimer's disease is a major public health issue that causes substantial impairment in cognition and function and 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	• Acetylcholinesterase inhibitors donepezil, rivastigmine, and galantamine, and the N-methyl-D-aspartate receptor antagonist memantine are approved for the treatment of Alzheimer's disease. These therapies affect the symptoms of the disease but do not change the progressive course of the disease. • Aducanumab and lecanemab are anti-amyloid beta-directed antibodies that received accelerated approval and traditional approval, respectively, and are indicated for the treatment of Alzheimer's disease, specifically patients with mild cognitive impairment or mild dementia stage of disease. • Antipsychotics are commonly prescribed to treat behavioral symptoms but are not approved for the treatment of Alzheimer's disease and are	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
	associated with increased mortality in older patients with dementia.	

Benefit	• The efficacy of donanemab in patients at the early stages of symptomatic Alzheimer's disease was evaluated in Study AACI
	  • Participants were randomized 1:1 to receive placebo or donanemab 700 mg administered as an IV infusion every 4 weeks for the first 3 doses, then 1400 mg every 4 weeks for up to 72 weeks. Donanemab treatment was switched to placebo based on amyloid PET levels measured at Week 24, Week 52, and Week 76
	  • The trial enrolled 1727 subjects: 853 in the donanemab arm and 874 in the placebo arm.
	  • Two key populations were defined: the overall population, including all enrolled subjects and a low/medium tau population based on tau pathology at baseline as measured by PET.
	  • The primary endpoint was the change from baseline in iADRS at Week 76. iADRS is a simple linear combination of two scores: ADAS-Cog 13 and ADCS-iADL.
	  • Key secondary endpoints were change from baseline to Week 76 in CDR-SB, ADAS-Cog 13, ADCS-iADL, and MMSE.
	  • Key pharmacodynamic endpoints included change from baseline in brain amyloid and tau disposition as measured by PET, brain volumes as measured by volumetric MRI, and plasma levels of neurofilament light chain (NfL), glial fibrillary acidic protein (GFAP), and phosphorylated tau (p-tau 181 and p-tau 217).
	• Treatment with donanemab demonstrated reduced clinical decline, as evidenced by a statistically significant treatment effect on change from baseline in iADRS compared to placebo in the low/medium tau population (3.25 [-35%], p<0.001) and the overall population (2.92 [-22%], p<0.001) at Week 76. The treatment effect can also be contextualized in terms of time saved, in which the time saved over 76 weeks was 4.4 months in the low/medium tau population and 1.4 months in the overall population.
		The results of Study AACI provide persuasive evidence of effectiveness of donanemab. The effect on CDR-SB represents a clinically meaningful reduction of clinical decline. The findings on the primary endpoint are supported by statistically significant results for all clinical endpoints, including endpoints capturing distinct information regarding cognitive decline and function. The treatment effect is supported by the consistently favorable results for the primary and secondary endpoints across subgroups of interest defined by demographic and baseline disease characteristics. Biomarkers reflecting brain amyloid plaque load and astrocytic activation support the observations on the clinical endpoints. Study AACG provides independent substantiation for the findings in Study AACI. Together, the results of these two adequate and well-controlled studies provide substantial evidence of effectiveness for donanemab for the treatment of Alzheimer's disease.
		
		There is no information on the need for dosing to maintain clinical benefit after amyloid PET thresholds for dose cessation have been reached. A clinical trial that assesses the safety and efficacy of a maintenance dosing regimen of donanemab will be requested as a post-marketing commitment (PMC).

Dimension	Evidence and Uncertainties	Conclusions and Reasons

	• Donanemab treatment also demonstrated a statistically significant reduction in decline on change from baseline CDR-SB compared to placebo in the low/medium tau population (-0.67 [-36%], p<0.001) and the overall population (-0.70 [-29%], p<0.001) at Week 76. Donanemab treatment resulted in an estimate of time saved over 76 months of 7.5 months in the low/medium tau population and 5.4 months in the overall population.
	• Statistically significant treatment effects in favor of donanemab were observed for all other multiplicity-controlled secondary clinical endpoints at Week 76 in the low/medium tau population: ADAS-Cog 13 (-1.52 [-32%], p<0.001) and ADCS-iADL (1.83 [-40%], p<0.001) and the overall population: ADAS-Cog 13 (-1.33 [-20%], p<0.001) and ADCS-iADL (1.70 [-28%], p<0.001).
	• Results were robust to sensitivity analyses.
	• The donanemab treatment arm had a statistically significant reduction in brain amyloid from baseline to Week 76 compared to the placebo arm (-86.4 Centiloid, p<0.0001).
	• Treatment effects on phosphorylated tau (p-tau 181 and p-tau 217) and GFAP supported the observations on clinical outcomes.
	• Favorable results for iADRS and CDR-SB were observed across subgroups of interest.
	• Study AACG was a smaller study (257 subjects: 131 in the donanemab arm and 126 in the placebo arm) of similar design
	  ◦ Donanemab treatment demonstrated a statistically significant reduction in brain amyloid plaque from baseline to Week 76 compared to placebo (-85.1 Centiloid, p<0.001).
	  ◦ The primary efficacy endpoint analysis, change from baseline in iADRS at Week 76, demonstrated a statistically significant treatment effect in the donanemab treatment arm compared to placebo (3.20 [-32%], p=0.042).
	  ◦ Favorable numerical results for secondary clinical endpoints were observed and were consistent with observations in Study AACI
	• During an off-treatment period, amyloid PET values began to increase with a median rate of 2.80 Centiloids/year. There is no data beyond the 76-week duration of Study 1 to guide whether additional dosing with donanemab may be needed for longer-term clinical benefit.	

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk and Risk Management	○ The safety database includes 2899 subjects exposed to at least one dose of donanemab at any dose. There were 2885 subjects with Alzheimer's disease in the mild cognitive impairment (MCI) or mild dementia stages of the disease exposed to donanemab intravenously. This includes 1912 subjects treated with donanemab 700 mg every 4 weeks for 3 doses followed by 1400 mg every 4 weeks for at least 6 months, 1057 subjects for at least 12 months, and 432 subjects for at least 18 months. ○ In Study AACI, there was an imbalance in deaths occurring within the 76 week placebo controlled on-study period in the donanemab-treated subjects (2.2%, 17/853) compared to placebo (1.2% (10/874), risk difference (95% CI) 0.6% (-0.6%, 1.8%). There were 3 deaths associated with ARIA and 1 of those deaths was caused by intracerebral hemorrhage in the setting of ARIA-H in a patient with superficial siderosis at baseline compared to none in placebo. ○ In the all-donanemab pool, there was an additional death associated with ARIA and an additional death associated with intracerebral hemorrhage that occurred in a patient with ARIA-E, with symptoms mimicking stroke who was treated with thrombolytic therapy. There was no other unusual cluster of deaths in the database. ○ The most common TEAEs in AACI (at least 5% and at least 2% greater than placebo) were ARIA-H microhemorrhage (25%), ARIA-E (24%), ARIA-H superficial siderosis (15%), headache (13%), and infusion-related reaction (9%). ○ ARIA was observed in 36% (307/853) of subjects treated with donanemab, compared to 14 % (122/874) of subjects on placebo in AACI. ○ The incidence of ARIA in AACI was higher in ApoE ε4 homozygotes (55% on donanemab vs. 22% on placebo) than in heterozygotes (36% on donanemab vs 13% on placebo) and noncarriers (25% on donanemab vs 12% on placebo). ○ Among subjects treated with donanemab, symptomatic ARIA-E occurred in 8% of ApoE ε4 homozygotes, compared with 7% of heterozygotes and 4% of noncarriers. ○ Serious events of ARIA occurred in 3% of	The safety database fulfills minimum ICH guidance. Risk management for ARIA can be achieved through clear product labeling and monitoring for ARIA, as described in the label. A Boxed Warning will describe the overall risk or ARIA with donanemab treatment and highlight the increased risk of ARIA, including symptomatic, serious, and severe radiographic ARIA, in ApoE ε4 homozygotes. The Boxed Warning will also describe fatal intracerebral hemorrhages that have occurred in subjects treated with donanemab. The Boxed Warning will also state that because ARIA-E can cause focal neurologic deficits that can mimic an ischemic stroke, clinicals should consider whether such symptoms could be due to ARIA before giving thrombolytic therapy in a patient treated with donanemab. The label will state that testing for ApoE ε4 status should be performed prior to initiation of treatment with donanemab to inform the risk of developing ARIA. A Warnings and Precautions Section 5.1 of the prescribing information will alert prescribers to the risk of ARIA and its symptoms when they occur and that the risk of ARIA, including symptomatic ARIA, was higher in ApoE ε4 homozygotes, providing details that support the Boxed Warning. Guidance regarding monitoring and implications regarding a finding of ARIA on subsequent dosing will be

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	ApoE ε4 homozygotes, and approximately 2% of heterozygotes and 1% of noncarriers. ○ Among subjects treated with donanemab who had ARIA-E, severe radiographic ARIA-E was greatest in Apo E ε4 homozygotes (3%, 4/143) compared to heterozygotes (2%, 9/452) or noncarriers (0.4%, 1/255). ○ Among subjects treated with donanemab who had ARIA-H, severe radiographic ARIA-H was greatest in Apo E ε4 homozygotes (22%, 31/143) compared to heterozygotes (8%, 38/452) or noncarriers (4%, 9/255). ○ Symptomatic ARIA occurred in 6% (52/853) of subjects treated with donanemab compared to none on placebo in AACI. The most common symptoms were headache and confusional state; other reported symptoms included dizziness, nausea, seizure, fatigue, gait disturbance, and tremor, consistent with symptoms reported for this class of drugs. ○ ARIA-E was observed in 24% (201/853) of subjects treated with donanemab compared to 2% (17/874) of subjects on placebo in AACI. Among the 853 subjects treated with donanemab, the maximum radiographic severity for ARIA-E was mild in 7%, moderate in 15%, and severe in 2%. The majority of ARIA-E radiographic events occurred early in treatment (within the first 7 doses). After detection, resolution occurred in 63 % of ARIA-E subjects by 12 weeks, 80% by 20 weeks, and in 83% by the end of the study overall. ○ ARIA-H was observed in 31% (263/853) of subjects on donanemab compared to 13% (111/874) of subjects on	provided in Section 2.3 of the prescribing information. MRI prior to the 5th, 7th, and 14th infusions will be utilized to identify asymptomatic ARIA. The Warning will describe the increased incidence of intracerebral hemorrhage in subjects taking donanemab with a concomitant antithrombotic medication, in particular an anticoagulant. • Prescribers will be advised to exercise additional caution when considering the administration of anticoagulants or thrombolytic agents (e.g., tissue plasminogen activator) to a patient already being treated with donanemab. • Patients will be advised to carry identification indicating that they are users of donanemab and that donanemab can cause ARIA with focal neurologic symptoms mimicking ischemic stroke. • The label will recommend caution when considering use of donanemab in patients that indicate an increased risk for intracerebral hemorrhage including the presence of an Apo E ε4 allele, findings on neuroimaging suggestive of CAA, or other lesions that could potentially increase the risk of intracerebral hemorrhage. • The label will recommend that treating clinicians consider whether focal neurologic deficits that can mimic ischemic stroke could be due to ARIA-E before giving thrombolytic therapy in a patient treated with donanemab.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	placebo in AACI. There was no imbalance in isolated ARIA-H for donanemab compared to placebo. o Intracerebral hemorrhage greater than 1 cm in diameter was reported in 0.5% (4/853) subjects on donanemab and in 0.2% (2/874) subjects on placebo in AACI. Fatal events of intracerebral hemorrhage in subjects taking donanemab were reported in AACI and in the long term extension (all donanemab pool) as noted above. The latter case was in the setting of symptoms of ARIA mimicking stroke, in which the subject was administered thrombolytic therapy in the absence of ischemic changes. o There incidence of ARIA-H in subjects who received donanemab and an antithrombotic medication was 30% compared to subjects who received no antithrombotic medication (29%). o The incidence of intracerebral hemorrhage was 0.6% (2/349) in subjects taking donanemab with a concomitant antithrombotic medication at the time of the event compared to 0.4% (2/504 subjects) in those who did not receive an antithrombotic. o Hypersensitivity reactions, including angioedema and anaphylaxis occurred in subjects treated with donanemab in AACI. o Infusion-related reactions occurred in 9% (74/853) of subjects on donanemab vs. 0.5% (4/874) in placebo-treated subjects in AACI. Infusion reactions were mostly mild (57%) or moderate (39%) in severity, and 70% occurred within the first 4 infusions. Symptoms associated with infusion reactions included chills, erythema, nausea/vomiting, dyspnea, sweating, elevated blood pressure (including 1 subject with a myocardial infraction within 5 minutes of starting the infusion), headache, chest pain, and low blood pressure. Sixty-eight percent (181/266) of subjects with an infusion reaction received	• The risk of ARIA, including the recommendation for Apo E ε4 testing and the risk for concomitant use of anticoagulants will also be addressed in the Medication Guide. Prescribers will be made aware of the risk of hypersensitivity in Section 5.2 and of infusion-related reactions in Section 5.3 of Warnings and Precautions. A history of a serious hypersensitivity reaction to donanemab will be a contraindication. This will also be addressed in the Medication Guide. Postmarketing requirements (PMRs) will be imposed to further characterize risk factors for adverse outcomes associated with ARIA. A postmarketing commitment (PMC) will be agreed upon for development of a test for Apo E ε4 genotype. Requested postmarketing vigilance will further characterize the uncertainties related to safety of donanemab.

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	subsequent infusions. Twenty-three percent (42/181) received preventative medication with subsequent infusions. The incidence of subsequent infusion-related reactions after a first event on donanemab was similar with (38%, 16/42) and without (41%, 57/139) preventative medication. Uncertainties • Patients with moderate or severe dementia were excluded from the key studies analyzed for review of safety; therefore, safety outcomes in these patients are unknown. • Whether the risk of ARIA or intracerebral hemorrhage in patients with AD treated with donanemab is higher in those with co-existing cerebral amyloid angiopathy (CAA) pathology is not known. Although the population that was treated would have included patients with CAA given that up to 90% of patients with AD are reported to have some degree of underlying CAA, it is currently not possible to prospectively identify those patients to understand how CAA impacts risk. • The safety of treating AD in patients with Down syndrome is not known. • The safety in underserved racial or ethnic populations is not fully characterized. • The optimal timing and frequency of MRI monitoring as a tool for mitigating ARIA is unknown. • The safety of treating patients with donanemab through episodes of radiographically mild ARIA-E with mild clinical symptoms is unknown. • The safety of treating patients with donanemab through episodes of radiographically mild, asymptomatic ARIA-H is unknown. • The safety of concomitant use of medications that increase bleeding risk is not well characterized. The risk of using donanemab in patients otherwise at risk for bleeding (e.g., the presence of an ApoE ε4 allele, the presence of CAA or other lesions such as aneurysm or vascular malformation) is not known.	

2. Background

This application under review is for donanemab (previously LY3002813), proposed for the treatment of Alzheimer's disease (AD). Donanemab is a humanized, immunoglobulin gamma 1 (IgG1) monoclonal antibody administered by intravenous (IV) infusion that targets insoluble N-truncated pyroglutamate 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 or any other country for any indication. The original application seeking accelerated approval was submitted based on data from a Phase 2 Study AACG of donanemab on May 18, 2022, and received a Complete Response (CR) letter on January 18, 2023 because the safety database was insufficient to adequately characterize the long-term safety of donanemab for the treatment of Alzheimer's disease. This application for traditional approval includes the results of the Phase 3 clinical trial (Study AACI) and is also intended to address the deficiencies outlined in the CR letter.

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

The pathologic hallmarks of AD are extracellular deposits of β-amyloid (Aβ), referred to as amyloid plaques, and intracellular aggregates of hyperphosphorylated tau in the form of neurofibrillary tangles. Accumulation of Aβ in the brain is generally thought to be the primary driver of the disease process, and precedes the accumulation of tau pathology and neurodegeneration. The pathophysiological changes and clinical manifestations of AD are progressive and occur along a continuum, and accumulation of Aβ may begin 20 years or more before symptoms arise (Vermunt et al., 2019). Based on these findings, National Institute on Aging—Alzheimer's Association (NIA-AA) research criteria have been recently developed for the diagnosis and staging severity of AD, based on neuropathologic biomarker-based findings of the presence or absence of amyloid, tau, and evidence of neurodegeneration (Jack et al., 2018). The 2024 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.

Approved AD treatments include cholinesterase inhibitors, the N-methyl-D-aspartate antagonist memantine, and anti-amyloid beta-directed antibodies. The acetylcholinesterase inhibitors donepezil, rivastigmine, and galantamine, are purported to address cholinergic deficits in AD by increasing acetylcholine levels in the central nervous system (CNS).

Memantine was approved in 2003, and is postulated to work by binding preferentially to N-methyl-D-aspartate (NMDA) receptor-operated cation channels to block persistent activation by the excitatory amino acid glutamate. These drugs provide modest benefits to patients with AD, but it is unclear whether these drugs slow or prevent neurodegeneration in patients with AD. In 2021, aducanumab, an anti-amyloid beta-directed antibody, was approved under the accelerated approval pathway based on reduction of amyloid plaques on PET imaging as a reasonably likely surrogate endpoint for the treatment of Alzheimer's disease, with use specifically recommended for patients with mild cognitive impairment or mild dementia stage of disease. Another anti-amyloid beta-directed antibody, lecanemab, received accelerated approval in January, 2023, followed by traditional approval in July, 2023. There remains a tremendous unmet need for therapies in AD that slow, halt, reverse, prevent, or cure the disease, with an important focus on drugs that target the underlying pathophysiology of AD in an effort to fundamentally affect the course of the disease.

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

In this BLA, the Applicant is seeking traditional approval of donanemab. This submission contains efficacy, safety, and biomarker data from Study AACI, a randomized, double-blind, placebo-controlled Phase 3 study in patients with MCI due to Alzheimer's disease or mild Alzheimer's disease dementia.

3. Product Quality

Product quality information for donanemab was previously reviewed in the initial submission. In the resubmission, the Applicant provided the results of the method validation for glycosylation profiling and the data and analyses used to set acceptance criteria along with updated specifications (i.e., including Oligosaccharide Profile). The Office of Pharmaceutical Quality (OPQ) review recommends approval and concludes that the data submitted are adequate to support the conclusion that the manufacture of KISUNLA is well-controlled and leads to a product that is pure and potent.

4. Nonclinical Pharmacology/Toxicology

No new nonclinical data were included in this resubmission. The nonclinical data was previously reviewed and found to be adequate to support approval in the review of the initial BLA submission by Dr. Hawver and Dr. Freed.

5. Clinical Pharmacology

An integrated Office of Clinical Pharmacology (OCP) review was written by Anantha Ram Nookala, Ph.D., Michael Bewernitz, Ph.D., Mohsen Rajabiabhari, Ph.D., Xiulian Du, Ph.D., Hobart Rogers, Ph.D., Jeffrey Kraft, Ph.D., Yow-Ming Wang, Ph.D., Atul Bhattaram, Ph.D., Bilal AbuAsal, Ph.D., Sreedharan Sabarinath, Ph.D., Hao Zhu, Ph.D., and Ramana Uppoor, Ph.D. The final OCP signatory was Mehul Mehta, Ph.D.

The clinical pharmacology team has concluded that the effectiveness of donanemab was supported by amyloid PET reduction, treatment-response relationships, and mechanistic support from downstream markers of Alzheimer's disease pathology (p-tau 217, p-tau 181, and GFAP).

In single doses ranging from 10 to 40 mg/kg, exposures (Cmax and AUC) of donanemab exhibited a proportional increase. Upon repeated dosing with 10 mg/kg or 20 mg/kg every 4 weeks, the AUC ratio from Day 141 to Day 1 was 1.06 and 1.26, respectively, indicating minimal accumulation.

The central volume of distribution is measured at 3.36 L. Donanemab undergoes degradation by proteolytic enzymes and is not expected to undergo renal elimination or metabolism by hepatic enzymes. The mean terminal half-life of donanemab is approximately 12.1 days, and its clearance is 0.0255 L/h. Age, sex, or race did not demonstrate a significant impact on the pharmacokinetics of donanemab. Although body weight and maximum anti-drug antibody (ADA) titer were found to influence donanemab pharmacokinetics, the resulting changes did not affect clinical efficacy. The review team concludes that no therapeutic individualization is necessary based on intrinsic and extrinsic factors such as age, race, sex, APOE4 genotype, baseline tau levels, renal impairment, hepatic impairment, or ADA status. For additional details, please also refer to the OCP review in DARRTS dated January 17, 2023.

Postbaseline, 793 participants in the donanemab group were evaluable for treatment-emergent ADAs (TE-ADAs) during the treatment period from Study AACI. Of these subjects, TE-ADAs were detected in 693 subjects; these subjects are therefore deemed ADA+ and the ADA incidence is 693/793 (87.4%). Neutralizing antibodies (NAbs) were detected in all the ADA+ subjects (693/693; 100%). The presence of TE-ADAs affected various PK measures, such as $C_{min,ss}$ and AUC_{ss}. Also, the presence of TE-ADAs affected amyloid plaque reduction; subjects with higher maximum ADA titer had less amyloid PET reduction compared to subjects with lower maximum ADA titer. However, the changes in amyloid PET associated

with high ADA titer did not translate into changes in efficacy measured on iADRS and CDR-SB up to week 76.

The review team raised concerns about the Applicant's proposal to stop treatment after plaque reduction because of limitations in the study, including reliance on a 12-month off-treatment period for calculating amyloid PET re-accumulation rate, data from a small subset of subjects for calculating amyloid PET re-accumulation rate beyond 76 weeks, lack of evaluation of long-term efficacy beyond 76 weeks, and exclusion of participants continuing on donanemab despite meeting dose cessation criteria.

The review noted that ApoE ε4 non-carriers and heterozygotes showed nominally higher treatment benefit and lower ARIA risk compared to homozygotes. Changes in amyloid PET and plasma biomarkers (p-tau217, p-tau181, and GFAP) reflected changes in clinical efficacy. However, given the positive trends in treatment benefit and biomarkers for all subgroups, the review team recommends dosing in all APoE ε4 genotypes, but describing efficacy and safety data in this subgroup in labeling to inform benefit-risk assessment.

The OCP review team recommends approval of the BLA.

6. Clinical/Statistical- Efficacy

Kevin Krudys, Ph.D., was the clinical reviewer for this application. Van Tran, Ph.D., was the reviewer for the Office of Biostatistics (OB), and Xiaofeng (Tina) Wang, MPH, was the statistical analyst, with concurrence from John Lawrence, Ph.D., Team Leader and James (Hsien-Ming) Hung, Ph.D., Division Director.

The efficacy of donanemab for this application was based primarily on the results of Study AACI. However, data from Study AACG was also considered to contribute to the assessment of efficacy.

Study AACI was a multicenter, randomized, double-blind, placebo-controlled, parallel-group study in subjects with early symptomatic Alzheimer's disease. A total of 277 centers across 8 countries enrolled subjects into the trial. Randomization was stratified by investigative site and tau pathology (low/medium or high). Tau PET levels at baseline were defined by visual read and quantitative standardized uptake value ratio (SUVR). The study included a screening period of up to 7 weeks, a 76-week placebo-controlled treatment period, and an immunogenicity and safety follow-up period of 44 weeks. Subjects were randomized to placebo or donanemab treatment in a 1:1 ratio in the placebo-controlled period.

Subjects who completed the placebo-controlled portion of the study had the option to enter the 78-week extension phase of the study.

A safety addendum was added to Study AACI to collect open-label safety data in up to approximately 1000 subjects with early symptomatic Alzheimer's disease who had evidence

of amyloid pathology. Subjects were to receive open-label donanemab at the dosing regimen described earlier. The inclusion and exclusion criteria were similar to those for the placebo-controlled period, except the tau PET criterion was removed. Subjects who did not meet the criteria for participation in the main study were allowed to screen for the addendum if screen failure was due to a non-eligible tau PET scan or non-eligible amyloid PET scan if the amyloid level was between 24.3 and 37.1 Centiloids. Clinical efficacy assessments were not collected in the safety addendum. Change in brain amyloid plaque deposition and blood-based biomarkers were included as endpoints.

Study Population

Study AACI enrolled subjects aged 60 to 85 years. Although the protocol did not specify a formal clinical diagnosis of AD, the inclusion criteria were consistent with a diagnosis of mild cognitive impairment (MCI) or mild dementia due to AD based on operationalized criteria from the 2018 National Institute on Aging at the National Institutes of Health and the Alzheimer's Association (NIA-AA) Research Framework for Alzheimer's disease (Jack et al. 2018). Subjects were required to have evidence of brain Aβ pathology by positron emission tomography (PET) scan with a value of ≥37 Centiloids and confirmed presence of tau on PET. Subjects were also required to have a Mini-Mental State Examination (MMSE) score between 20 and 28 (inclusive) and a gradual and progressive change in memory function reported by the patient or informant for ≥6 months. Subjects were excluded for any neurological disease, other than AD, that may affect cognition or ability to complete the study, current serious or unstable illnesses including cardiovascular, hepatic, renal, gastroenterologic, respiratory, endocrinologic, psychiatric, immunologic, or hematologic disease, or history of clinically significant multiple or severe drug allergies. Subjects were also excluded if a brain MRI performed at screening showed evidence of any of the following: presence of ARIA-E, >4 cerebral microhemorrhages, more than 1 area of superficial siderosis, any macrohemorrhage, severe white matter disease, or evidence of a significant abnormality that would suggest another potential etiology for progressive dementia.

There were two primary analysis populations based on tau PET imaging with flortaucipir: 1) low/medium tau level population (defined by visual assessment and SUVR of ≥1.10 and ≤1.46), and 2) combined population of low/medium plus high tau (defined by visual assessment and SUVR >1.46) population.

Dosing

IV infusions of donanemab or placebo were administered over a minimum of 30 minutes every 4 weeks for up to 72 weeks. Subjects were to receive 700 mg every 4 weeks for the first 3 doses, then 1400 mg every 4 weeks up to Week 72. Double-blind dose cessation of donanemab was guided by amyloid PET levels measured at Week 24, Week 52, and Week 76. Subjects were switched to placebo if their amyloid level was <11 Centiloids on PET at any single visit, or ≥11 to <25 Centiloids on PET at 2 consecutive visits. The Applicant argues that amyloid plaque is the only amyloid species engaged by donanemab and therefore there is no reason to continue dosing once amyloid plaque has been reduced below a certain level.

Specific dose modification criteria for ARIA were not established. In the event of clinically significant ARIA-E or ARIA-H, the investigator could choose to suspend treatment and monitor the patient using serial MRIs. Upon resolution of ARIA-E, stabilization of ARIA-H, and resolution of any associated symptoms, the investigator could use their judgment to reinitiate treatment. For subjects who developed ARIA and had dose suspension during titration, the investigator could elect to reinitiate and continue dosing with 700 mg or continue with the planned titration to 1400 mg.

Temporary discontinuation of treatment was also allowed if a short-term treatment with an excluded medication was necessary, secondary to hospitalization, personal or exceptional circumstance, or to evaluate the treatment impact on an uncertain AE. In the case of a systemic hypersensitivity suspicious for an anaphylactic reaction related to treatment administration, the subject was to be permanently discontinued from treatment.

Primary Clinical Endpoint

The primary endpoint was the change from baseline in integrated Alzheimer's Disease Rating Scale (iADRS) at Week 76. The iADRS is a composite measure that combines the ADAS-Cog 13 and ADCS-iADL, and its score ranges from 0 to 144 with lower scores indicating greater disease severity. The iADRS was developed to assess function and cognition in a single measure that is more sensitive to change and treatment effects in patients at the early stages of the disease (Wessels et al. 2015).

In the meeting minutes of the March 2, 2021, Type C Meeting, the Division stated that, "we do not agree that a statistically significant treatment effect on the iADRS, unaccompanied by a valid statistically significant treatment effect on its two components, is acceptable for use as a primary efficacy assessment. Thus, the iADRS should not be used as your primary efficacy assessment." The Division further noted that it "was not persuaded as to whether the effects of an intervention, such as donanemab, on the iADRS could be considered necessarily clinically meaningful or reflective of effects of its individual components." The Division reiterated its concerns with the use of iADRS as the primary endpoint at the December 22, 2022, Type B Meeting.

Secondary Clinical Endpoints

CDR-SB

The CDR-SB assesses three domains of cognition (memory, orientation, judgment/problem solving) and three domains of function (community affairs, home/hobbies, personal care) using semi-structured interviews with the patient and a reliable companion or informant. A qualified rater uses interview data and clinical judgment to assign scores for each domain ranging from none=0, questionable = 0.5, mild = 1, moderate = 2 to severe = 3. The personal care domain does not include the 0.5 score. Scores from each domain are summed to provide the CDR-SB value ranging from 0 to 18, with higher scores indicating greater disease severity.

At the March 2, 2021, Type C Meeting the Division noted that, "As study AACI has already been initiated with the CDR-SB as its prospectively designated primary outcome, our advice is that this approach be retained."

Alzheimer's Disease Assessment Scale- cognitive subscale (ADAS-Cog 13)
The ADAS-Cog is a cognitive assessment consisting of clinical ratings and cognitive tasks measuring disturbances of memory, language, and praxis. The scale ranges from 0 to 85, with higher scores indicating greater disease severity.

Alzheimer's Disease Cooperative Study – instrumental Activities of Daily Living Scale (ADCS-iADL)
The ADCS-ADL is a rater-administered questionnaire for informants that consists of 23 items. Informants are asked whether the patient attempted each item during the past 4 weeks and to rate the patient's performance level. The iADL is a subset consisting of 17 items measuring instrumental activities of daily living (rather than basic activities of daily living) which are thought to be more sensitive at earlier stages of the disease. The iADL score ranges from 0 to 59, with lower scores indicating greater impairment.

Mini-Mental State Examination
The MMSE is a widely used performance-based assessment of cognitive ability consisting of 11 tasks evaluating orientation, word recall, attention and calculation, language, and visuospatial functions. The scores from the 11 tests are summed to obtain a total score, which ranges from 0 to 30, with lower scores indicating greater cognitive impairment. It is often used as a screening assessment in clinical practice or as a staging instrument for trial inclusion and is also used as an efficacy assessment in clinical trials. The MMSE was listed as a secondary endpoint, but was not included in the prespecified statistical testing hierarchy.

Exploratory Endpoints
The following were included as exploratory endpoints:

- The digit symbol substitution test (DSST) is a computer-administered neuropsychological test administered to the subject.
- Time to a clinical worsening event was defined as meeting the following criteria at 2 consecutive visits
    - Any increase in CDR global score
    - ≥1 point increase in CDR-SB for subjects with MMSE at screening of 27-30 or a ≥2 points increase for subjects with MMSE at screening of 20-26
    - 5 points decrease in iADRS for subjects with MMSE at screening of 27-30 or 9 points decrease for subjects with MMSE at screening of 20-26
- The probability of not progressing, which was defined as having a CDR-SB change from baseline ≤0.

Pharmacodynamic Endpoints

- Change from baseline in brain amyloid deposition through 76 weeks as measured by ^{18}F-florbetapir or ^{18}F-florbetaben PET. The amyloid PET analysis was the SUVR calculated for a composite summary region of 6 cortical regions (anterior cingulate, posterior cingulate, medial orbital frontal, lateral temporal, lateral parietal, and precuneus) with whole cerebellum as a reference region. A negative change from baseline in SUVR indicates a reduction in amyloid burden and a negative treatment difference (donanemab minus placebo) favors donanemab. SUVR values were converted to the Centiloid scale (Navitsky et al. 2018) for analysis and reporting.
- Change from baseline in brain tau deposition at 76 weeks as measured by ^{18}F-flortaucipir PET. Global tau was measured as MUBADA (Multi-block Barycentric Discriminant Analysis) SUVR. An Alzheimer's disease signature region weighted SUVR and regional tau were measured in the frontal, parietal, and posterior lateral temporal regions with a cerebellar region as the reference.
- Change from baseline in brain volumes as measured by volumetric magnetic resonance imaging (vMRI) for the following regions: bilateral hippocampal, total brain, and ventricular.
- Change from baseline in plasma levels of neurofilament light chain (NfL), glial fibrillary acidic protein (GFAP), and phosphorylated tau (p-tau 181 and p-tau 217).

AACI Safety Addendum

A safety addendum was added to Study AACI to collect open-label safety data in up to approximately 1000 subjects with early symptomatic Alzheimer's disease who had evidence of amyloid pathology. Subjects were to receive open-label donanemab at the dosing regimen described earlier. The inclusion and exclusion criteria were similar to those for the placebo-controlled period, except the tau PET criterion was removed. Subjects who did not meet the criteria for participation in the main study were allowed to screen for the addendum if screen failure was due to a non-eligible tau PET scan or non-eligible amyloid PET scan if the amyloid level was between 24.3 and 37.1 Centiloids. Clinical efficacy assessments were not collected in the safety addendum. Change in brain amyloid plaque deposition and blood-based biomarkers were included as endpoints.

Statistical Analysis Plan:

The original Statistical Analysis Plan (SAP) was issued on November 1, 2021, and was amended twice, with the final version implemented on April 20, 2023, prior to unblinding of the study data.

A Natural Cubic Spline (NCS) model with 2 degrees of freedom (NCS2) was used to assess the difference between treatment groups in iADRS at Week 76. For the NCS2 model, 2 knots were placed at the minimum and maximum observations times and 1 knot was placed at the median observation time. The baseline estimates of iADRS were restricted to be the same for the placebo and donanemab treatment groups. Study visit was treated as a continuous variable with values equal to weeks between baseline and post-baseline visits. The model included fixed effects for NCS expansion terms (2 terms), NCS basis expansion term-by-treatment interaction (2 terms), baseline age, use of AD medication at baseline (yes or no),

and pooled investigator. Baseline tau category was included as a covariate in the model applied to the overall population.

A number of additional analysis methods were described in the SAP. A mixed model repeated measures (MMRM) model was also used to analyze change from baseline in clinical endpoints at Week 76 with fixed effects terms for baseline score, baseline score-by-visit interaction, pooled investigator, treatment, visit, treatment-by-visit interaction, use of AD medication at baseline (yes or no), and age at baseline. Baseline tau category was included as a covariate in the model applied to the overall population. MMRM was the primary analytical approach for CDR-SB.

Bretz's graphical approach was used to control the study-wise type I error rate for the primary and key secondary hypotheses at a 2-sided alpha level of 0.05. For the primary analysis, the initial 2-sided alpha level was set to 0.04 for the low/medium tau population and 0.01 for the overall population. See Dr. Tran's statistical review for further details.

Subgroup Analyses

Subgroup analyses for iADRS, CDR-SB, ADAS-Cog 13, ADCS-iADL, MMSE, amyloid PET, tau PET, and plasma biomarkers were planned for the following pre-defined groups:

- Age group (<65, 65-74, and ≥75 years)
- Sex (male, female)
- Race (While, Black or African American, Asian)
- Ethnicity (Hispanic or Latino, not Hispanic or Latino)
- ApoE ε4 carrier status (carrier, non-carrier)
- ApoE ε4 genotype (non-carrier, heterozygous carrier, homozygous carrier)
- Clinical staging at screening (MMSE 20-26, MMSE 27-28)
- Baseline brain tau category (low/medium, high)
- Baseline tau SUVR tercile defined by screening MUBADA SUVR
- BMI (<25, 25-30, ≥30 kg/m^2)

Results

A total of 8240 subjects were screened for entry into the study and 1736 subjects were randomized. There were 9 subjects who were randomized (2 placebo, 7 donanemab) but discontinued before receiving study treatment. A total of 137 subjects (52 placebo, 85 donanemab) were not included in the evaluable efficacy population for the primary endpoint because they did not have a baseline assessment and/or at least one post-baseline iADRS assessment or were discontinued before receiving study treatment. There was an imbalance in the proportion of subjects discontinuing due to AEs (2.4% placebo, 5.8% donanemab) as well as a larger number of subjects in the donanemab arm who chose to withdraw from the study. There were also 12 subjects (7 donanemab, 5 placebo) who did not complete a final visit prior to data lock. Table 1 contains information regarding demographic and disease

characteristics for the low/medium and overall populations. Demographic characteristics were balanced across the treatment arms and generally representative of the patient population except for an under-representation of African American and Hispanic subjects. Overall, 72% of subjects were enrolled in the United States.

Table 1: Study AACI Baseline Demographic and Disease Characteristics (Randomized Population)

	Low/Medium Tau Population			Overall Population		
	Placebo N=594 n(%)	Donanemab N=588 n(%)	Total N=1182 n(%)	Placebo N=876 n(%)	Donanemab N=860 n(%)	Total N=1736 n(%)
Sex						
Male	273 (46.0%)	263 (44.7%)	536 (45.3%)	373 (42.6%)	367 (42.7%)	740 (42.6%)
Female	321 (54.0%)	325 (55.3%)	646 (54.7%)	503 (57.4%)	493 (57.3%)	996 (57.4%)
Age Group						
<65 years	34 (5.7%)	31 (5.3%)	65 (5.5%)	88 (10.0%)	88 (10.2%)	176 (10.1%)
65-74 years	256 (43.1%)	265 (45.1%)	521 (44.1%)	402 (45.9%)	414 (48.1%)	816 (47.0%)
>=75 years	304 (51.2%)	292 (49.7%)	596 (50.4%)	386 (44.1%)	358 (41.6%)	744 (42.9%)
Race						
White	539 (90.7%)	522 (88.8%)	1061 (89.8%)	807 (92.1%)	781 (90.8%)	1588 (91.5%)
Black or African American	17 (2.9%)	17 (2.9%)	34 (2.9%)	21 (2.4%)	19 (2.2%)	40 (2.3%)
American Indian or Alaska Native	0	1 (0.2%)	1 (0.1%)	0	2 (0.2%)	2 (0.1%)
Asian	38 (6.4%)	48 (8.2%)	86 (7.3%)	47 (5.4%)	57 (6.6%)	104 (6.0%)
Multiple	0	0	0	1 (0.1%)	0	1 (0.1%)
Missing	0	0	0	0	1 (0.1%)	1 (0.1%)
Ethnicity						
Not Hispanic or Latino	558 (93.9%)	555 (94.4%)	1113 (94.2%)	825 (94.2%)	813 (94.5%)	1638 (94.4%)
Hispanic or Latino	26 (4.4%)	24 (4.1%)	50 (4.2%)	37 (4.2%)	35 (4.1%)	72 (4.1%)
Not reported	9 (1.5%)	8 (1.4%)	17 (1.4%)	12 (1.4%)	11 (1.3%)	23 (1.3%)
Missing	1 (0.2%)	1 (0.2%)	2 (0.2%)	2 (0.2%)	1 (0.1%)	3 (0.2%)
Country						
United States	417 (70.2%)	415 (70.6%)	832 (70.4%)	632 (72.1%)	620 (72.1%)	1252 (72.1%)
Poland	57 (9.6%)	53 (9.0%)	110 (9.3%)	82 (9.4%)	77 (9.0%)	159 (9.2%)
United Kingdom	17 (2.9%)	14 (2.4%)	31 (2.6%)	23 (2.6%)	16 (1.9%)	39 (2.2%)
Canada	53 (8.9%)	46 (7.8%)	99 (8.4%)	73 (8.3%)	64 (7.4%)	137 (7.9%)
Australia	1 (0.2%)	9 (1.5%)	10 (0.8%)	4 (0.5%)	13 (1.5%)	17 (1.0%)
Japan	36 (6.1%)	40 (6.8%)	76 (6.4%)	43 (4.9%)	45 (5.2%)	88 (5.1%)
Netherlands	5 (0.8%)	6 (1.0%)	11 (0.9%)	9 (1.0%)	13 (1.5%)	22 (1.3%)
Czech Republic	8 (1.3%)	5 (0.9%)	13 (1.1%)	10 (1.1%)	12 (1.4%)	22 (1.3%)
Laboratory ApoE4 status						
Carrier	427 (71.9%)	421 (71.6%)	848 (71.7%)	621 (70.9%)	598 (69.5%)	1219 (70.2%)
Heterozygote	327 (55.1%)	331 (56.3%)	658 (55.7%)	475 (54.2%)	455 (52.9%)	930 (53.6%)
Homozygote	100 (16.8%)	90 (15.3%)	190 (16.1%)	146 (16.7%)	143 (16.6%)	289 (16.6%)
Non-Carrier	164 (27.6%)	166 (28.2%)	330 (27.9%)	251 (28.7%)	259 (30.1%)	510 (29.4%)
Missing	3 (0.5%)	1 (0.2%)	4 (0.3%)	4 (0.5%)	3 (0.3%)	7 (0.4%)
Baseline CDR-SB						

	Low/Medium Tau Population			Overall Population		
	Placebo N=594 n(%)	Donanemab N=588 n(%)	Total N=1182 n(%)	Placebo N=876 n(%)	Donanemab N=860 n(%)	Total N=1736 n(%)
Mean (SD)	3.7 (2.0)	3.7 (2.1)	3.7 (2.1)	3.9 (2.1)	4.0 (2.1)	3.9 (2.1)
Median	3.5	3.5	3.5	3.5	3.5	3.5
Min, Max	(0.0, 15.0)	(0.0, 11.0)	(0.0, 15.0)	(0.0, 15.0)	(0.0, 11.0)	(0.0, 15.0)
Missing	3.0 (0.5%)	8.0 (1.4%)	11.0 (0.9%)	7.0 (0.8%)	15.0 (1.7%)	22.0 (1.3%)
Baseline CDR global score						
0.5	387 (65.2%)	382 (65.0%)	769 (65.1%)	532 (60.7%)	514 (59.8%)	1046 (60.3%)
1	185 (31.1%)	177 (30.1%)	362 (30.6%)	308 (35.2%)	304 (35.3%)	612 (35.3%)
2	16 (2.7%)	19 (3.2%)	35 (3.0%)	25 (2.9%)	25 (2.9%)	50 (2.9%)
0	3 (0.5%)	2 (0.3%)	5 (0.4%)	4 (0.5%)	2 (0.2%)	6 (0.3%)
Missing	3 (0.5%)	8 (1.4%)	11 (0.9%)	7 (0.8%)	15 (1.7%)	22 (1.3%)
Baseline MMSE						
Mean (SD)	22.8 (3.8)	23.0 (3.6)	22.9 (3.7)	22.2 (3.9)	22.4 (3.8)	22.3 (3.9)
Median	23.0	23.0	23.0	22.0	23.0	22.0
Min, Max	(6.0, 30.0)	(12.0, 30.0)	(6.0, 30.0)	(6.0, 30.0)	(11.0, 30.0)	(6.0, 30.0)
Missing	0	5.0 (0.9%)	5.0 (0.4%)	5.0 (0.6%)	10.0 (1.2%)	15.0 (0.9%)

Source: adsl.xpt (created by reviewer)

Primary Endpoint

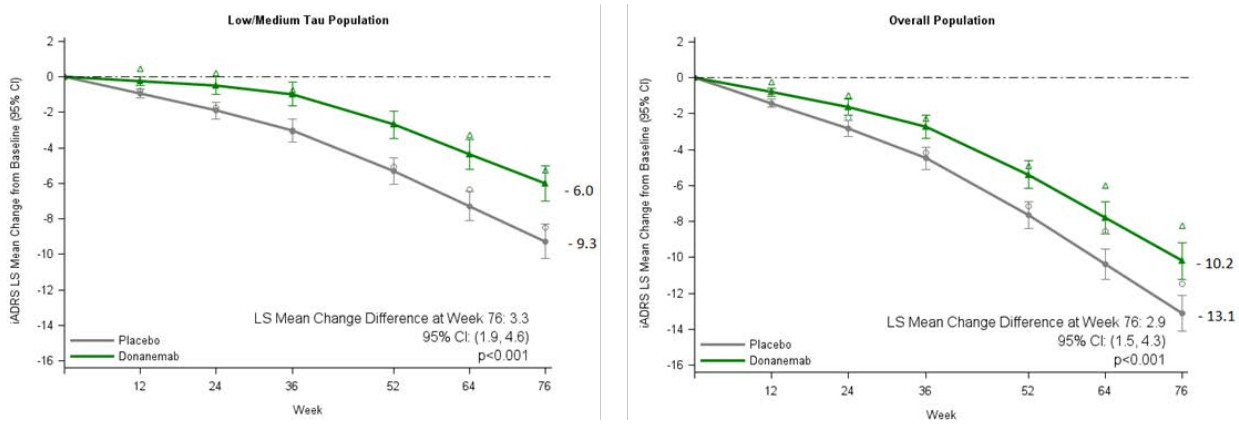
The primary efficacy endpoint analysis, change from baseline in iADRS at Week 76, demonstrated a statistically significant treatment effect in the donanemab treatment arm compared to placebo in the low/medium tau population (3.25[-35%], p<0.001) and the overall population (2.92[-22%], p<0.001) (Table 2). Nominal statistical significance was reached by Week 12 and maintained through Week 76 (Figure 1).

Table 2: Primary Endpoint Analysis, Study AACI

	Low/Medium Tau		Overall	
	Placebo (N=560)	Donanemab (N=533)	Placebo (N=824)	Donanemab (N=775)
Baseline iADRS				
n	560	533	824	775
Mean	105.95	105.92	103.82	104.55
Change from Baseline in iADRS at Week 76				
n	444	418	653	583
Adjusted mean	-9.27	-6.02	-13.11	-10.19
Standard error	0.49	0.50	0.50	0.53
Difference from placebo		3.25		2.92
95% CI for difference		(1.883, 4.618)		(1.508, 4.331)
% difference vs. placebo		-35.1%		-22.3%
p-value (compared with placebo)		<0.001		<0.001

Source: Tables AACI.5.2 and AACI.5.3 from Study AACI CSR

Figure 1: Longitudinal Change From Baseline for iADRS (left – low/medium tau population, right – overall population)



Source: Statistical Analyst.
NCS2 estimates with 95% CI are represented as filled symbols with CI bands. Observed estimates are represented as unfilled symbols.
Abbreviations: CI, confidence interval; iADRS, Integrated Alzheimer's Disease Rating Scale; LS, least squares; NCS2, natural cubic splines with two degrees of freedom

To address the potential effect of functional unblinding due to ARIA or infusion reactions, the Applicant compared the results of the primary analysis to results using a reduced dataset in which all assessments after occurrence of ARIA-E or infusion reaction were excluded. The results were similar and thus do not suggest a systematic bias due to functional unblinding. It is important to reiterate that steps were taken in the protocol to minimize functional unblinding, specifically blinding of the rater to adverse events. Also, ARIA and infusion reactions also occurred in the placebo arm, suggesting that investigators could not, with complete accuracy, know the subject's treatment group based on occurrence of such an event.

The treatment effect on the primary endpoint was contextualized in terms of time saved using PMRM. Donanemab treatment resulted in a statistically significant estimate of time saved of 4.4 (1.87, 6.85) months (p<0.001) in the low/medium tau population and 1.4 (0.46, 2.3) months (p=0.004) in the overall population over the 18-month treatment period. Proportional time slowing was assumed in the overall population but not the low/medium tau population.

Secondary Endpoints

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

Donanemab treatment demonstrated a statistically significant reduction in decline on change from baseline CDR-SB compared to placebo in the low/medium tau population (-0.67 [-36%], p<0.001) and the overall population (-0.70 [-29%], p<0.001). Nominal statistical significance

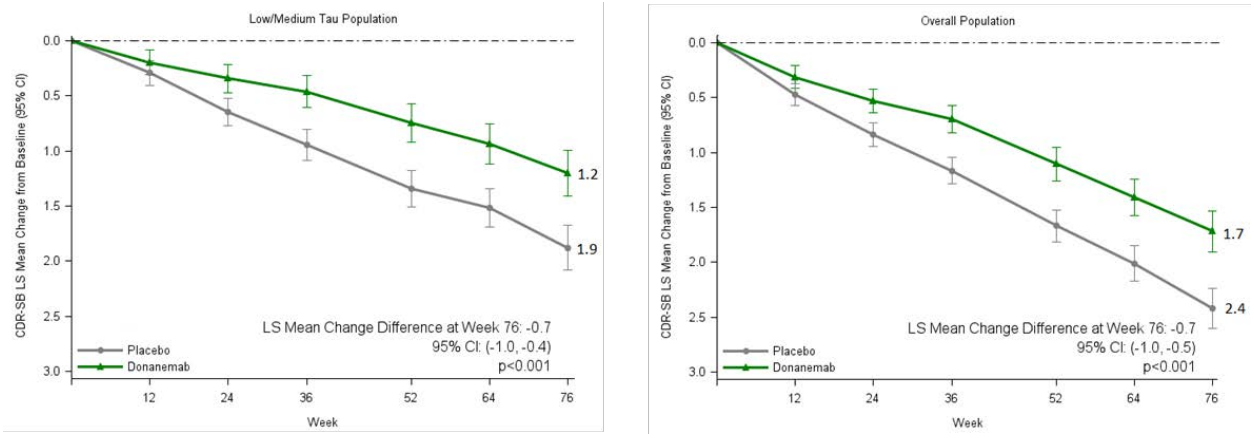
was reached by Week 24 in the low/medium tau population and Week 12 in the overall population and maintained through Week 76.

Table 3: Study AACI Secondary Endpoint Analysis (CDR-SB)

	Low/Medium Tau		Overall	
	Placebo (N=569)	**Donanemab** (N=546)	**Placebo** (N=838)	**Donanemab** (N=795)
Baseline CDR-SB				
N	569	546	838	794
Mean	3.64	3.72	3.89	3.92
Change from Baseline in CDR-SB at Week 76				
n	459	424	672	598
Adjusted mean	1.88	1.20	2.42	1.72
Standard error	0.102	0.105	0.092	0.096
Difference from placebo		-0.67		-0.70
95% CI for difference		(-0.95, -0.40)		(-0.95, -0.45)
% difference vs. placebo		-36.0%		-28.9%
p-value (compared with placebo)		<0.001		<0.001

Source: Tables AACI.5.6 and AACI.5.7 from Study AACI CSR

Figure 2: Longitudinal Change from Baseline for CDR-SB (left – low/medium tau population, right – overall population)



Source: Statistical Analyst.
Abbreviations: CDR-SB, Clinical Dementia Rating – Sum of Boxes; CI, confidence interval, LS, least squares, MMRM, mixed model for repeated measures; N, number of participants; n, number of participants with a given variable; SD, standard deviation; SE, standard error

The treatment effect on CDR-SB was contextualized in terms of time saved using PMRM. Donanemab treatment resulted in a statistically significant estimate of time saved of 7.53 (5.69, 9.36) months (p<0.001) in the low/medium tau population and 5.44 (3.90, 6.98)

months (p<0.001) in the overall population over the 18-month treatment period. Proportional time slowing was assumed in both populations.

Donanemab treatment resulted in a reduction in change from baseline as measured on the ADAS-Cog 13 compared to placebo in the low/medium tau population (-1.52 [-32%], p<0.001) and the overall population (-1.33 [-20%], p<0.001). A treatment effect was also observed for change from baseline in the ADCS-iADL compared to placebo in the low/medium tau population (1.83 [-40%], p<0.001) and the overall population (1.70 [-28%], p<0.001). Nominal statistical significance was reached by Week 12 and maintained through Week 76 for both endpoints.

Sensitivity Analyses

Several sensitivity analyses, including ones requested by the statistical reviewer, demonstrated that the statistically significant results were mostly robust to different modeling assumptions. Dr. Tran notes that sensitivity analyses of iADRS and CDR-SB with the unfavorable outcome of death imputed as the worst score produced a similar and statistically significant treatment effect compared to the primary analysis. Analysis with death imputed as worst score for ADAS-Cog 13 and time to substantial decline in CDR global score, however, did not achieve statistical significance when compared to p-value cutoffs that were multiplicity controlled. Tipping point analysis to assess sensitivity of the CDR-SB primary analysis to missing data assumptions showed that the results in both the low/medium and overall populations were not statistically significance near the delta pair (0, 0.5), where 0.5 is the minimum within-subject scale increment change.

Subgroup Analyses

Prespecified subgroup analyses were performed across demographic and baseline characteristics. With the exception of the small subgroups of Black/African American race for iADRS and Hispanic/Latino ethnicity for CDR-SB, findings are generally consistent with the overall population estimate and favor treatment with donanemab.

Exploratory Endpoints

No treatment effect was observed for the DSST in either the low/medium tau population or the overall population. Results for MMSE showed less change from baseline at Week 76 in the donanemab treatment group than in subjects on placebo in the low/medium tau population (0.48 [-23%], 95% CI [0.09, 0.87]) and the overall population (0.47 [-16%], 95% CI [0.10, 0.84]).

Donanemab treatment reduced the risk of progression on the CDR global score by 39% with a hazard ratio of 0.61 (0.47, 0.80), p<0.001 in the low/medium population and by 37% with a hazard ratio of 0.63 (0.51, 0.77), p<0.0001 in the overall population. A total of 100 (18%) donanemab-treated subjects and 163 (28%) placebo-treated subjects had substantial decline in the CDR global score in the low/medium tau population and 186 (23%) donanemab-treated subjects and 288 (34%) placebo-treated subjects had substantial decline in the overall population.

A total of 47% (42%, 51%) of donanemab-treated subjects in the low/medium tau population were non-progressors (CDR-SB change from baseline ≤0) at Week 52 compared to 29% (25%, 33%) of placebo-treated subjects (p<0.00001). In the overall population, 36% (33%, 40%) of donanemab-treated subjects were non-progressors at Week 52 compared to 23% (20%, 26%) of placebo-treated subjects.

Pharmacodynamic Endpoints

Donanemab treatment demonstrated a statistically significant effect on change from baseline in brain amyloid plaque as measured by PET and reported as Centiloids at Week 76 in the low/medium tau population (-88.2, p<0.0001) and the overall population (-86.4, p<0.0001). Amyloid plaque levels were assessed at Weeks 24, 52, and 76, and subjects were switched to placebo if their amyloid level was <11 Centiloids on PET at any single visit, or ≥11 to <25 Centiloids on PET at 2 consecutive visits. At Weeks 24, 52, and 76, the proportion of participants in the donanemab treatment arm who met dose stopping criteria based on amyloid PET results was 17%, 43.5%, and 60%, respectively.

No treatment effect was observed in change from baseline to Week 76 in frontal tau deposition compared with placebo in the low/medium tau population (0.002, p=0.97) or the overall population (-0.004, p=0.45). Similarly, no treatment effect was observed in either population in AD-signature-weighted SUVR tau deposition or in exploratory regional (i.e., posterior lateral temporal and parietal) tau endpoints.

Donanemab treatment was associated with a decrease in whole brain volume and an increase in ventricular volume at Week 76. Similar changes have been observed with other monoclonal antibodies targeting aggregated brain amyloid. Various hypotheses for these volume changes have been proposed (e.g., fluid shifts due to amyloid removal), but the cause is still unclear. Although it is possible that the findings could represent atrophy, given the favorable results on clinical endpoints observed in Study AACI, the clinical relevance of these changes is unclear. In contrast to whole brain and ventricular volume changes, there was a trend for a reduction in volume loss in the hippocampus with donanemab treatment.

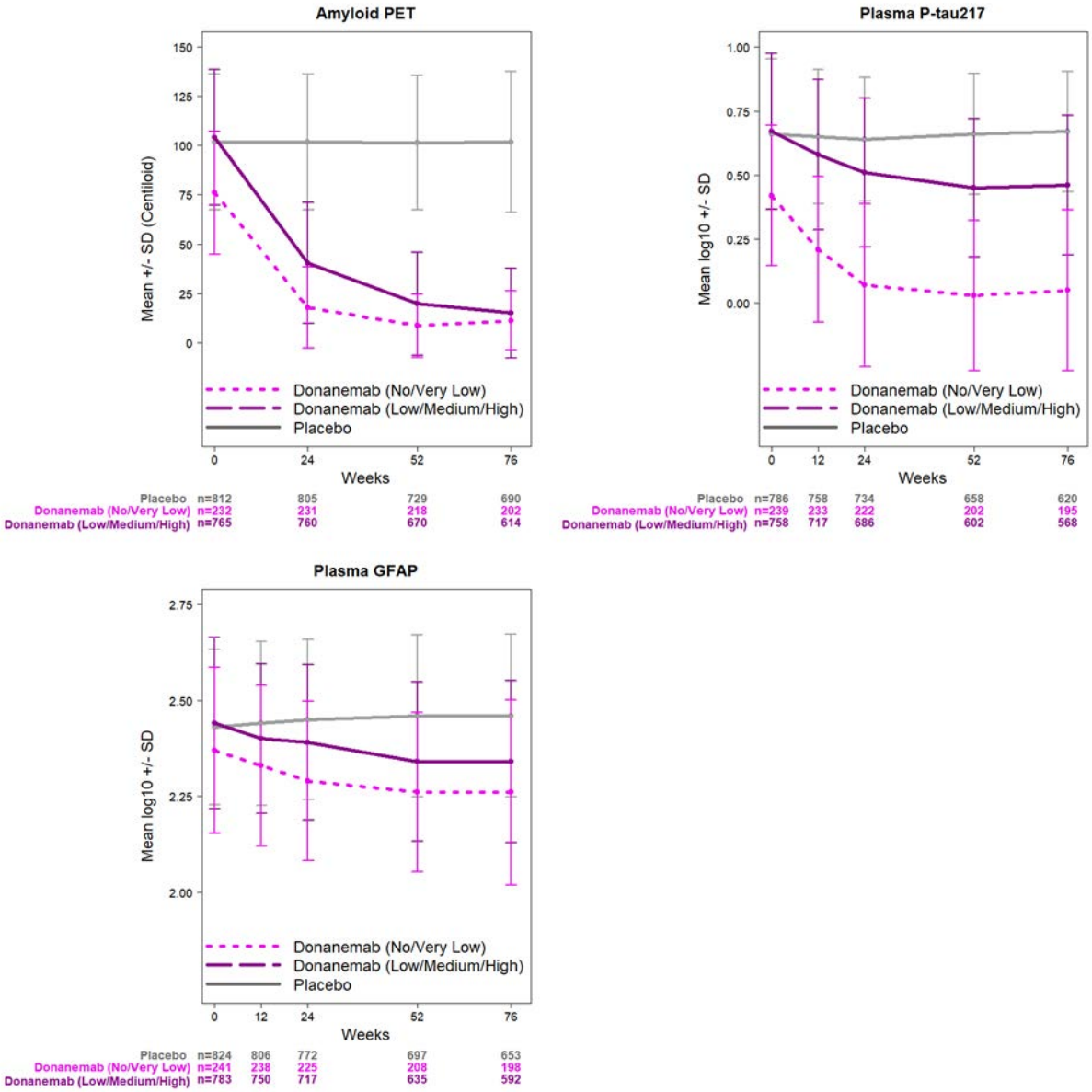
Donanemab treatment demonstrated a statistically significant effect on change from baseline in plasma p-tau 217 at Weeks 24 and 76 (p<0.0001). Donanemab treatment was also associated with a decrease in p-tau 181 and GFAP compared to placebo at Week 76. No treatment difference was observed for plasma NfL at Week 76, but a larger increase was observed in the donanemab arm compared to placebo at Weeks 12 and 24.

Results from AACI Safety Addendum

Approximately 200 participants enrolled in the single-arm, open-label, safety addendum to Study AACI. This addendum included a cohort of participants who failed the tau PET entry criterion for the double-blind portion of the study. Compared to participants with low/medium or high tau enrolled in Study AACI, participants with no or very low tau had lower baseline levels of brain amyloid, plasma p-tau 217 and GFAP, consistent with their

earlier disease stage. Reductions in amyloid, plasma p-tau 217 and GFAP from baseline were generally similar in the two populations (Figure 1).

Figure 3: Biomarker Results in Subjects with No or Very Low Tau (Study AACI Safety Addendum) Compared to Subjects with Low/Medium/High Tau (Study AACI)



Source: Created by Dr. Krudys from adgfap.xpt, adept.xpt, adptau.xpt, and adsl.xpt in 11/21/2023 regulatory response

Results from Study AACG

Study AACG was reviewed during the original submission for accelerated approval and the results will only be briefly summarized below.

A total of 1995 participants were screened for entry into the study and 272 participants were randomized (126 placebo, 131 donanemab, 15 donanemab in combination with LY3202626). Of the 257 participants randomized to the placebo or donanemab arms, 32 participants (25%) receiving placebo and 37 participants (28%) receiving donanemab discontinued from the study. At baseline, the mean age of randomized participants was 75 years with a range of 61 to 86 years. Forty-seven percent of participants were male and 95% were white.

The primary efficacy endpoint analysis of change from baseline in iADRS at Week 76 demonstrated a statistically significant treatment effect in the donanemab treatment arm compared to placebo (3.2; 95% CI 0.1, 6.3; p=0.04; 32% reduction). The difference between the donanemab group and the placebo group in the change from baseline in CDR-SB at Week 79 did not reach statistical significance (−0.4; 95% CI −0.8, 0.1; p=0.14; 23% reduction). Differences between the donanemab group and the placebo group in the change from baseline at 76 weeks were 1.9 (95% CI −3.6. −0.1; 39% reduction) for ADAS-Cog 13, 1.2 (95% CI −0.8, 3.2; 23% reduction) for ADCS-iADL, and 0.6 (−0.4, 1.7) for MMSE. Donanemab treatment demonstrated a reduction in brain amyloid plaque reported as Centiloid and compared to placebo at Week 76 (placebo least square (LS) mean change from baseline 0.9; donanemab LS mean change from baseline -84.1; treatment LS mean change difference −85.1; 95% CI −92.7, −77.4).

Biostatistics Review Conclusions

Dr. Tran concludes that Study AACI demonstrated evidence of effectiveness on the iADRS and Study AACG also provided evidence of effectiveness on the iADRS, but also notes the potential for the primary analysis of CDR-SB in Study AACI to be sensitive to missing data assumptions. The biostatistics review team recommends approval.

Efficacy Conclusions

Donanemab was originally reviewed for accelerated approval based on the results of the Phase 2 Study AACG. The clinical efficacy review for that submission recommended accelerated approval based on a finding of substantial evidence of effectiveness on a reasonably likely surrogate endpoint. The application received a Complete Response, however, because the safety database was insufficient to adequately characterize the long-term safety of donanemab for the treatment of Alzheimer's disease. In response to the Complete Response letter of January 18, 2023, the Applicant submitted the results of the pivotal study, Study AACI. Because accelerated approval was never granted for the original submission, Study AACI is reviewed in the context of providing substantial evidence of effectiveness for traditional approval rather than simply verifying clinical benefit. The results of Study AACG are also considered in this review as contributing to the evidence of effectiveness. The application was also discussed with the Peripheral and Central Nervous System Advisory Committee at a meeting held on June 10, 2024.

Study AACI demonstrated consistent and robust clinical benefit on all primary and secondary clinical endpoints. The primary efficacy endpoint analysis, change from baseline in iADRS at

Week 76, demonstrated a statistically significant treatment effect in the donanemab treatment arm compared to placebo in the low/medium tau population (3.25[-35%], p<0.001) and the overall population (2.92[-22%], p<0.001). Nominal statistical significance was reached by Week 12 and maintained through Week 79. Results were robust across sensitivity analyses. Statistically significant results favoring donanemab were observed for the secondary endpoint CDR-SB. Donanemab resulted in a reduction in change from baseline as measured on the CDR-SB in both the low/medium tau population (-0.67 [-36%], p<0.001) and the overall population (-0.70 [-29%], p<0.001) as compared to placebo.

Statistically significant results favoring donanemab were also observed for the secondary endpoints ADAS-Cog 13 (-1.52 [-32%], p<0.001 in the low/medium tau population and -1.33 [-20%], p<0.001 in the overall population) and ADCS-iADL (1.83 [-40%], p<0.001 in the low/medium tau population and 1.70 [-28%], p<0.001)in the overall population). Donanemab treatment also demonstrated a statistically significant treatment effect on change from baseline in brain amyloid as measured by PET and reported as Centiloids at Week 79 (-59.1, p<0.00001).

Study AACG also contributes to evidence of effectiveness for donanemab. Although a smaller study, it is considered an adequate and well-controlled study. The study demonstrated statistically significant results on primary endpoint of iADRS with numerical trends on the ADAS-Cog-13 and ADCS-iADL components and also on the CDR-SB that were consistent in magnitude to those observed in AACI. Study AACG provides independent confirmation of the results of Study AACI.

The Division had previously advised against the use of the iADRS as a primary endpoint as it was unclear that changes on the scale would necessarily be driven by clinically meaningful effects on both cognition and daily function and not driven by an effect on only one component. In order to consider the iADRS clinically meaningful, strong positive effects would need to be demonstrated on both components, ADAS-Cog 13 (cognition) and ADCS-iADL (function). As such the Division previously recommended that the study either use the CDR-SB as a sole primary endpoint or ADAS-Cog 13 and ADCS-iADL as co-primary efficacy measures. As Study AACI showed statistically significant effects on the ADA-Cog 13, ADCS-iADL, and the CDR-SB, the previously expressed concerns with the iADRS as a primary endpoint have been addressed within the context of this application. However, the acceptability of the iADRS in other AD drug development programs will also need to take into consideration the effects on its component scales and consistency with other assessments in the study.

In addition to being statistically robust and persuasive, the results on the clinical endpoints in Study AACI appear to be clinically meaningful. Although the Division previously raised questions regarding the clinical meaningfulness of the iADRS, the consistent effects across multiple secondary endpoints, and notably the CDR-SB and the ADCS-iADL that assess the impacts of cognition on daily function, support the clinical meaningfulness of the results of the study. Additionally, it is anticipated that the treatment benefit from a drug that impacts

underlying disease biology will increase over time and that is, in fact, what is demonstrated in Study AACI.

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

Together, Studies AACI and AACG provide substantial evidence of effectiveness of donanemab for the treatment of Alzheimer's disease, initiated in persons with AD in the mild cognitive impairment and mild dementia stages of the disease. The clinical reviewer, clinical pharmacology review team, and the biostatistics review team all support traditional approval of the application. However, there were some unique elements of the study design that require additional consideration for description in labeling.

The Applicant does not propose a requirement for confirmation or quantification of tau pathology in the prescribing information despite excluding subjects with no or very low tau from the controlled portions of Studies AACG and AACI and prioritizing a low/medium tau population in the statistical analysis of Study AACI. Dr. Krudys concludes it is reasonable to generalize the efficacy results from the population studied in Study AACI across the spectrum of tau burden based on the following observations. Subjects who meet criteria for AD based on confirmed presence of brain amyloid and cognitive impairment have the same underlying pathophysiology of disease regardless of the tau burden. The course of the disease is also progressive for all tau levels, although a higher tau burden reflects a later stage of disease that may progress more rapidly. The pharmacodynamic effect of the drug is expected to be similar in patients who are amyloid positive, regardless of tau status, and in fact subjects with no or very low tau treated during the safety addendum showed similar reduction in amyloid plaque on PET and on other pharmacodynamic markers as those with higher tau levels. Furthermore, modeling suggests that clinical benefit may be even greater in patients with lower tau burden. Safety was similar across the spectrum of tau burden. This issue was discussed at the advisory committee meeting and most committee members thought biomarker effects in patients enrolled in the Study AACI safety addendum supported efficacy in patients with no or very low tau. There was also general consensus that requiring tau PET in labeling would be impractical to implement and would impede access to treatment. Given these considerations, selection of patients based on tau PET imaging will not be recommended in the prescribing information.

The Applicant has proposed a dosing regimen where dosing with donanemab may be stopped based on reduction of amyloid plaques on amyloid PET imaging below a level

generally consistent with a negative visual read. The Applicant has proposed that dosing cessation based on amyloid levels be a "consideration" and not a "requirement" for the dosing regimen. The advisory committee was asked to opine on the scientific and/or clinical considerations that may factor into a decision to stop or continue dosing with donanemab. The committee members agreed that a dosing regimen guided by reduction of amyloid plaque on PET imaging was an innovative component of the clinical trial design that could provide potential benefits for compliance and reduced burden on patients and the health care system. However, they also noted challenges in obtaining PET imaging to confirm amyloid reduction, both due to access issues to imaging facilities and reimbursement. Members were in agreement that more long-term data is needed to address questions on duration of amyloid clearance, how frequently patients would need to be monitored after stopping donanemab, when treatment should be re-initiated, and potential adverse effects of stopping and restarting therapy.

Taking this advice into consideration, the prescribing information will describe that cessation of dosing based on minimal amyloid levels on PET imaging may be considered, but that there is no data on the efficacy or safety of subsequent dosing with donanemab after reduction to minimal levels is achieved. To address the gaps in knowledge about the need for re-initiation of dosing or a maintenance dosing regimen, a post-marketing commitment (PMC) will be issued to conduct a randomized, double-blind, controlled trial of donanemab in participants with early-stage Alzheimer's disease that assesses a maintenance dosing regimen compared to placebo for a period of at least 2 years after completion of an initial dosing regimen in which dosing is stopped based on reduction of amyloid. This trial may be conducted through cross over of participants in TRAILBLAZER-ALZ 3 upon completion of that trial.

7. Safety

Dr. Natalie Branagan performed the safety review for the submission with CDTL, Dr. Ranjit Mani, and Deputy Director for Safety, Dr. Sally Yasuda. Drs. Ping Li, Fengyu Zhao, Yueqin Zhao, and Mat Soukup in the Division of Biometrics VII (DBVII) provided statistical analyses of mortality.

Exposures and Adequacy of the Safety Database

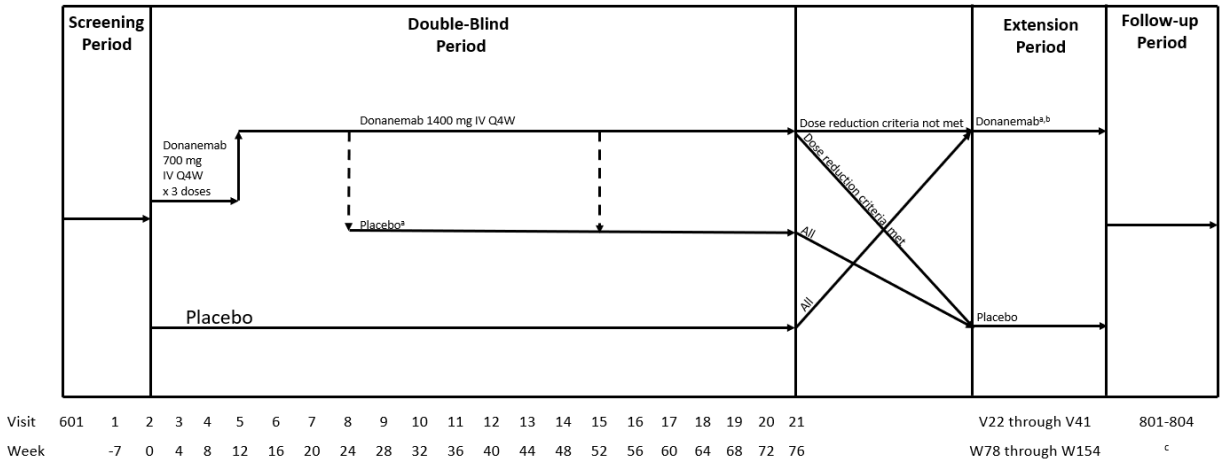
The primary safety data are from the placebo-controlled portion of Study AACI. The pooled placebo-controlled periods of Study AACI and Study AACG (placebo-controlled pool), the long-term extension period of Study AACI, the Safety Addendum of Study AACI, and Studies AACH Part B (open-label follow on study for subjects who received placebo in AACG), AACI Safety Addendum (ongoing, direct enrollment, open-label study addendum), and AACN-Dona Cohort (ongoing, randomized, open-label active comparator study) provide supportive safety data. Study AACG was reviewed in the original submission.

The safety database includes 2899 subjects (2893 with Alzheimer's disease) exposed to at least one dose of donanemab at any dose. Eight subjects were dosed subcutaneously in a

Phase 1 study. There were 2885 subjects with Alzheimer's disease exposed to donanemab intravenously. The placebo controlled period of AACI included 853 subjects exposed to donanemab and 874 exposed to placebo. At the highest clinically relevant dose that is the dose in the proposed labeling (700 mg every 4 weeks for 3 doses followed by 1400 mg every 4 weeks)[2], 1912 subjects were exposed to donanemab for 6 months, 1057 subjects for 12 months, and 432 subjects for at least 18 months, as of the 90 day safety update. The ICH guidelines for drugs intended for long-term use of at least 300 subjects for 6 months and 100 subjects for 1 year at the clinically relevant dose are met. The safety database is adequate to assess the safety of donanemab at a dose of 700 mg every 4 weeks for 3 doses followed by 1400 mg every 4 weeks.

Of note, the dosing regimen for donanemab was 700 mg IV dosed every 4 weeks for the first 3 doses followed by 1400 mg IV every 4 weeks thereafter up to 72 weeks, with cessation of dosing guided by amyloid PET levels measured at Week 24, Week 52, and Week 76. The ongoing open-label extension period AACI and open-label studies AACH Part B, AACI Safety Addendum, and AACN-Dona Cohort had the same titration and allowance for stopping treatment. The study scheme is shown in Figure 4, below.

Figure 4: Schematic for AACI



Dr. Branagan notes that in AACI, approximately 12% of subjects randomized to donanemab had switched to placebo by weeks 28 through 52, and approximately 32% had switched to placebo by weeks 56-72. The switch to placebo could complicate interpretation of adverse reactions overall in subjects assigned to donanemab vs placebo; those subjects are evaluated as randomized in the present review. Of note, the labeling will recommend that consideration be given to stopping dosing based on reduction in amyloid plaques to minimal levels on PET imaging.

[2] Also includes subjects who received 1400 mg for the first three doses, prior to a protocol amendment changing the first 3 doses to 700 mg.

In the placebo controlled period of AACI, approximately 80% of the population treated with donanemab in the safety analysis set were from North America (US and Canada). The mean age was approximately 73 years (range 59 to 86 years). Approximately 90% (n=765) were at least 65 years old and 41% (n=351) were at least 75 years old. Fifty-seven percent were women. Seventeen percent (143/853) of subjects were ApoE ε4 homozygotes, 53% (452/853) were heterozygotes, and 30% (255/853) were noncarriers[3]; this is representative of the general population of patients with Alzheimer's disease. White subjects accounted for 91%, Hispanic or Latino accounted for 4%, 7% were Asian, and Black or African American accounted for 2%. The population demographics were similar for donanemab and placebo. As Dr. Branagan notes, although at an increased risk for Alzheimer's disease[4], Black subjects and Hispanic subjects are under-represented compared to the general United States population.[5] In addition, Dr. Branagan notes that patients enrolled in the studies had MCI or mild AD, and that patients with more advanced disease or other serious or unstable illnesses were not included in these studies. Therefore, as Dr. Branagan notes, the safety outcomes may underestimate the impact of adverse events in a broader population.

Dr. Branagan considered the Applicant's translation of adverse events from verbatim terms to preferred terms to be adequate. She notes that the protocols for the clinical studies did not have case report forms for collection of ARIA-H symptoms and that in AACG, ARIA-H was not reported as an adverse event but captured as an MRI finding; therefore, in agreement with the Applicant, Dr. Branagan notes that analyses of findings from MRI, as she has reviewed, would better represent the frequency of ARIA-H than would reliance on the adverse reaction datasets.

Quality issues have been addressed subsequent to information requests, with no outstanding substantive issues identified by Dr. Branagan that would impact data analysis and safety review.

Deaths

Mortality analyses were based on an on-study approach and included all deaths reported by the end of the study period (76 weeks for the placebo-controlled period of Study AACI), regardless of whether the patient discontinued from the study period. In the 76 week placebo-controlled on-study period of AACI, deaths occurred in 2.2% (17/853) subjects randomized to donanemab and in 1.2% (10/874) subjects randomized to placebo as shown in the table below from the DBVII review. Three deaths were related to ARIA. As Dr. Branagan notes, the non-ARIA related mortality at 76 weeks occurred in 1.8% (14/853) subjects

[3] 3 subjects had unknown carrier status.
[4] https://www.alz.org/media/Documents/alzheimers-facts-and-figures.pdf
[5] https://www.census.gov/quickfacts/fact/table/US/PST045223

randomized to donanemab and in 1.2% (10/874) randomized to placebo, risk difference (95% CI) 0.6% (-0.6%, 1.8%), hazard ratio (95% CI) 1.49 (0.66, 3.35).[6]

Table 5. Mortality Assessment of Trial AACI (Safety Population); On-study

n, (%[a])	Donanemab N = 853	Placebo N = 874	RD (95% CI)	HR[b] (95% CI)
Mortality at 76 weeks	17 (2.2%)	10 (1.2%)	1.0% (-0.3%,2.3%)	1.80 (0.83, 3.94)

Source DBVIII Statistical Reviewer's analysis using ADSL.XPT in SN120

[a] Kaplan-Meier estimates of cumulative incidence

[b] Hazard ratio estimate from Cox PH model without covariate adjustment

Abbreviations: HR = hazard ratio, RD = risk difference

Data from subjects who continued into the LTE or were newly started on donanemab from placebo in the Safety Addendum were included in the All-Donanemab pool. In the all-donanemab pool, deaths occurred in 1.3% of subjects (37/2802).

ARIA-related deaths occurred in 3 subjects (subjects I5T-MC-AACI-(b) (6) and I5T-MC-AACI-(b) (6), as well as subject I5T-MC-AACI-(b) (6) who had had an intracerebral hemorrhage in the setting of ARIA-E and ARIA-H) in the placebo controlled portion of AACI and in one subject, I5T-MC-AACI-(b) (6) in the all-donanemab pool, which are attributed to use of donanemab. There were no ARIA-related deaths in the placebo arm of study AACI.

The role of donanemab in the intracerebral hemorrhage leading to death, in the setting of ARIA-E and ARIA-H in subject I5T-MC-AACI-(b) (6) in the placebo-controlled portion of AACI, cannot be ruled out, although the subject had risk factors for intracerebral hemorrhage suggestive of CAA. An additional death from cerebral hemorrhage occurred in subject I5T-MC-AACI-(b) (6) in the all-donanemab pool, in whom the role of donanemab cannot be ruled out, although this subject had risk factors for intracerebral hemorrhage (superficial siderosis and the presence of an ApoE ε4 allele). The patient was administered thrombolytic therapy in the setting of ARIA-E with symptoms mimicking stroke and then developed a fatal intracerebral hemorrhage (see details in next section).

Dr. Branagan also notes one death due to thalamus hemorrhage in a patient with a history of hypertension. She notes deaths from subarachnoid hemorrhage, head injury, and multiple fractures, in subjects who had falls, and notes that falls are among the most commonly reported SAEs. There was no other unusual cluster of deaths.

As Dr. Branagan notes in her review, the evaluation of safety, including mortality, in the placebo-controlled period of AACI and the placebo-controlled pool was limited by the percentage of subjects who withdrew from the study (approximately 26% of subjects in the

[6] DBVII Statistical Reviewer's analysis using SUBJINFO.XPT in SN161, where mortality incidences are Kaplan-Meier estimates of cumulative incidence.

donanemab arm and 20% on placebo in the placebo-controlled period of AACI), and vital status at Week 76 was not captured for these patients by the Applicant. The analyses of safety may underestimate the incidence of adverse reactions with donanemab.

As Dr. Branagan notes, the Division requested that the Applicant retrieve additional mortality information among patients who discontinued Study AACI prior to Week 76 and for whom the vital status was not available at the time of the 90-Day safety update. Using a third-party vendor, the Applicant retried vital status through publicly available records and databases, social media, and traditional media. Information on cause of death is still not available. Among 352 participants (198 for donanemab and 154 for placebo) whose vital status was unknown, the vital status of 184 participants was retrieved: 118 for donanemab and 66 for placebo, respectively. Among the participants with retrieved vital status information, two participants randomized to donanemab died within 76 weeks and six participants randomized to placebo died within 76 weeks, resulting in updated mortality of 2.3% on donanemab (19/853) and 1.9% on placebo (16/874).

Deaths related to ARIA

Deaths associated with ARIA are described in detail below.

Subject I5T-MC-AACI-(b) (6) was a 72 year-old female, Apo E ε3/ ε4, with declining cognition for several weeks prior to the onset of ARIA-E, presenting with confusion, agitation, forgetfulness, short attention span, garbled speech, and disorientation, who was hospitalized and diagnosed with the SAE of ARIA-E with severe vasogenic edema on Day 66, with the last dose of study drug (3rd dose) on Day 56. CT of the head on Day 66 noted the following in the impression: extensive vasogenic edema throughout the right cerebral hemisphere, and probably some within the left occipital lobe remains stable with no discrete enhancing mass. A CT scan without contrast showed a potential subacute right-sided stroke and multifocal areas of vasogenic edema in the right cerebral hemisphere with some confluence and mass effect. A CT angiogram of the head and neck showed a nonspecific multifocal area of vasogenic edema in the right cerebral hemisphere. An EEG on Day 69 was reported as nonspecific moderately severe encephalopathy. A CT scan of the head on Day 72 showed "a sliver of hyperdensity within the right posterior and anterior frontal lobe sulci along the vertex suspicious for new foci of subarachnoid hemorrhage" and extensive vasogenic edema as described on Day 66. Three days later the patient was discharged to hospice care and died on Day 80. The patient's screening MRI showed focal lesions of white matter disease and did not show presence of ARIA-E, cerebral microhemorrhages, cerebral hemorrhages, or superficial siderosis. There were no post-screening MRIs received by the investigator. Cerebral edema was listed as cause of death. The investigator listed the outcome of ARIA-E as fatal. Autopsy results have not been made available to the site.

Subject I5T-MC-AACI-(b) (6) was a 72 year-old male, Apo E ε3/ ε3 with a history that included bowel cancer, brain trauma, migraines, hypertension, and hypercholesterolemia, who was hospitalized for right hemiplegia and aphasia on Study Day 72 and diagnosed with

severe cerebral hemorrhage and hemorrhagic stroke with mass effect. Blood pressure ranged between 106-13/65-73 mm Hg during study visits prior to the event. The SAE of ARIA-H (severe) was also reported that day. He had taken several acetylsalicylic acid tablets (quantity and dose unknown) at the onset of aphasia. The second and last dose of blinded study medication had been 43 days prior to symptom onset. He complained of a mild headache on Days 46 thru 56, and Day 59. On Day 46 he was reported to have mild ARIA-E. MRI on Day 71 showed mild ARIA-E (left parietal, right occipital, and right temporal lobes), ARIA H (based on presence of a new microhemorrhage), superficial siderosis in the left frontal lobe (increased from baseline of 50 mm to 65 mm), and in the right occipital, right parietal, and right temporal non-hippocampal areas (all measuring < 8 mm). Approximately four months before his baseline MRI, the patient had an MRI that showed "hemorrhagic focal area left caudate nucleus (cavernoma?)." Three weeks later CT angiography showed no arteriovenous malformation. His baseline MRI had shown superficial siderosis in the left frontal lobe (50 mm) and presence of white matter disease with beginning of confluence of lesions according to the central read, with the local read of the MRI noting moderate to marked amount of increased T2 signal identified in the periventricular, deep and subcortical white matter of both cerebral hemispheres. A CT scan in the emergency room showed a large left parietal intraparenchymal hemorrhage and vasogenic edema, left frontotemporoparietal intraparenchymal hemorrhage of amyloid appearance with midline shift (5mm), and an adjacent subarachnoid hemorrhage. A repeat CT scan the same day showed a hematoma in the left posterior parietal region, measuring 5.5 x 4.3 cm. A CT angiogram of the carotid arteries showed < 50% stenosis of the left carotid artery and < 30% of the right carotid artery. The patient became comatose and was transferred to palliative care and died on Day 75. The cause of death on the death certificate was hemorrhagic stroke and ARIA-H. An autopsy was not performed. As noted in the review of the original submission, the Agency considers this death to be categorized as an intracerebral hemorrhage. The presence of superficial siderosis at baseline is suggestive of cerebral amyloid angiopathy (CAA) which increases the risk of intracerebral hemorrhage.[7] A potential role for an interaction between donanemab and underlying CAA cannot be determined. The relatedness of intracerebral hemorrhage to the use of donanemab in this setting is uncertain.

Subject I5T-MC-AACI-(b) (6) (identified in original review as (b) (6) /Manufacturer Report # US202211015256) was a 75 year-old White male with a history including chronic kidney disease stage 3, hypertension, hyperlipidemia, type 2 diabetes mellitus, aortic arteriosclerosis, balance disorder, and heterozygous for ApoE ε4, and who had a previous episode of ARIA-E and ARIA H on Study Day 79 after 3 doses of donanemab for which dosing was temporarily stopped until Day 202 with events shown in the table below.

Study Day	**Events**

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

79	Visit 5 (Week 12) The patient was noted to have severe ARIA-E on a scheduled MRI (right frontal; right temporal, non-hippocampal; right parietal; right occipital) and more than 10 new microhemorrhages (11 total). The study drug was temporarily discontinued on this day. The patient had had three doses of study drug with the most recent dose occurring 15 days before severe ARIA-E was diagnosed by MRI.
107	An unscheduled MRI showed that the ARIA-E had decreased in size and was still severe. Additionally, the patient had developed more than 10 new microhemorrhages (23 total microhemorrhages).
135	An unscheduled MRI showed moderate ARIA-E and 1 new microhemorrhage (24 total microhemorrhages).
167	An MRI showed mild ARIA-E and no new microhemorrhages.
195	An MRI showed resolution of ARIA-E and no new microhemorrhages.
202	Study drug was resumed (Week 28, Visit 9) at a dose of 700 mg or placebo equivalent
209	The patient developed intermittent headaches and the study drug was temporarily discontinued.
232	An MRI showed no ARIA-E and no new microhemorrhages.
253	The study drug was resumed at a dose of 700 mg with the 5th infusion.
331	Starting with 8th infusion, the dose was adjusted to 1400 mg.

The subject presented to the ER (on Study Day 427) with nausea (moderate) and vomiting (moderate) and was admitted for serious ARIA-E (severe) and ARIA-H (severe) and died 18 days later. On Study Day 413, severe ARIA-E was reported and the participant was reported to have a confusional state (moderate) and balance disorder (moderate). The patient had received 10 doses of study drug prior to presentation to the ER, with the most recent dose on Day 399. An unscheduled MRI obtained four days before presentation to the ER (Study Day 423) showed severe ARIA-E (right frontal; left frontal; right temporal, right occipital, right parietal; left parietal) and more than 10 new microhemorrhages (43 total microhemorrhages). At baseline, the patient's MRI showed no ARIA-E, microhemorrhages, superficial siderosis, or macrohemorrhage. Vital signs upon admission to the ER included an elevated blood pressure (213/107 [units not reported]), temperature 36.9 (units not reported), pulse of 75 (units not reported), and respiratory rate of 18 (units not reported). A neurological exam showed left sided weakness with some contracture, left sided neglect, altered mental status, and somnolence. The impression from a CT scan was diffuse vasogenic edema within the right cerebral hemisphere with 2 mm of right to left midline shift. An MRI the following day showed ARIA-E with extent greater than 10 cm and involvement in multiple areas of the brain (right frontal, right temporal, nonhippocampal, right parietal, right occipital, left frontal, left parietal) and greater than 10 microhemorrhages. The patient was started on dexamethasone and ondansetron and discharged to hospice that day (Study Day 428). Ten days later, he was discharged to a skilled nursing facility where he passed 9 days later (SAE preferred term: death). No autopsy was performed. Death was reported due to

symptomatic ARIA-E and symptomatic ARIA-H.

Subject I5T-MC-AACI-(b) (6) was a 77 year-old male with past medical history of AD, hypertension, hyperlipidemia, coronary artery disease, atrial flutter, prostate cancer, ApoE e3/ε4 genotype, who was hospitalized for difficulty walking, worsening confusion, severe headache, severe nausea, severe dizziness, severe unstable gait, and severe visual impairment on Study Day 694 with the SAE of ARIA-E (severe). His screening MRI showed 1 microhemorrhage. He had received his fifth dose of donanemab 23 days before hospitalization. An MRI on Study Day 696 showed moderate T2 hyperintense lesion in the right occipital lobe with vasogenic edema and mild mass effect. Two days later, the patient was transferred to another hospital and experienced hypoxia, was transferred into the intensive care unit, and was obtunded. He was reported to have seizures (generalized seizure, episodes of arm tremor that looked like seizure, and episodes of gaze deviation suggestive of seizure). The following day, he was started on intravenous methylprednisolone 1000 mg/day for five days and then prednisone 60 mg daily. During the hospitalization, he also received acyclovir, levetiracetam, lorazepam, valproic acid, and lacosamide. He underwent a lumbar puncture, which yielded 3 mL of cerebrospinal fluid (CSF), with findings of protein 104, glucose 80, white blood cells 23, red blood cells 3200 (reference ranges not provided). A repeat lumbar puncture showed two nucleated cells and was negative for herpes simplex virus. Serum and CSF autoimmune encephalitis panels were negative and serum John Cunningham (JC) virus was positive. CSF JC virus testing was not performed. On Study Day 716, he was discharged to hospice and then returned the same day for comfort care because of worsening obtundation and near comatose state. Seven days later (Study Day 723), an MRI showed decreased abnormal T2/FLAIR signal in the right occipital lobe with resolution of surrounding mass effect and sulcal effacement. Five days later, he was discharged to a nursing home and two days later he died (Study Day 730). The cause of death was reported as secondary to symptomatic ARIA-E, aggravated by seizures.

Subject I5T-MC-AACI-(b) (6) was a 70 year-old male with past medical history of AD, ApoE e3/ε4 carrier, and dyspepsia, and screening MRI showing focal lesions of white matter disease, who developed headache and slurred speech and was hospitalized for the SAE of ischemic stroke (severe) on Study Day 702, 13 days after the 5th dose of donanemab. Blood pressure on admission was 146/83 mmHg with a heart rate of 65 beats per minute. An ECG showed sinus rhythm. Labs showed a normal international normalized ratio (0.98, reference range of 0.86-1.09) and normal activated partial thromboplastin time (22.9 sec, reference range 22.1 - 33.9). The most recent study blood pressure reading (9 days prior to the ischemic stroke) had been normal at 122/77 mmHg. Blood pressures readings at study visits when the subject was on treatment with donanemab ranged between 113-133/68-77 mmHg (Visits 23 through 26). Concomitant medications at the time of the event included alprazolam, escitalopram, memantine, pantoprazole, and vitamin D. A CT angiogram of the head and neck vessels did not show significant stenosis, dissection, aneurysm, or large vessel occlusion. A CT of the head/brain without contrast did not identify an acute intracranial process. A CT brain perfusion showed no asymmetric fixed or reversible ischemic defect. A tele-neurology consult recommended that the subject receive tissue plasminogen activator (tPA). An hour after

receiving tenecteplase, the subject developed altered mental status. A repeat CT scan showed multiple hemorrhages in the bilateral hemispheres. The SAE of intracranial hemorrhage was reported (severe). The subject was given factor I, factor VIII, factor XIII and Von Willebrand factor to reverse the effect of tenecteplase. An MRI performed after Tenecteplase administration (centrally read) showed presence of severe ARIA-E in the left parietal lobe and bilateral frontal and occipital lobes; superficial siderosis in the left parietal (70 mm), occipital (50 mm), and temporal (40 mm) lobes; macrohemorrhage in the left temporal lobe (50 mm), left occipital (50 mm), left parietal (35 mm), and right frontal (30 mm); and bilateral intraventricular hemorrhage. On the same day (Study Day 702), the SAE of ARIA-E (severe) was reported. Four days later, the subject died due to bilateral intraparenchymal hemorrhage and acute hypoxic respiratory failure. No autopsy was performed. The most recent MRI prior to the SAE of intracranial hemorrhage was on Study Day 663 and showed focal lesions of white matter disease. As Dr. Branagan notes, the presence of superficial siderosis and the presence of an ApoE ε4 allele are risk factors for the events of ARIA-E and intracerebral hemorrhage. She also notes that the presenting symptoms of headache and slurred speech may have been secondary to ARIA-E, rather than ischemic stroke. Although a role for donanemab cannot be completely ruled out, the relationship of donanemab to the intracerebral hemorrhage in this setting of treatment with tenecteplase is uncertain.

Other Notable Deaths

Thalamus hemorrhage, I5T-MC-AACI- (b) (6) in a 77 year old male with a history including hypertension and stroke who developed the SAE of thalamus hemorrhage (severe) on Study Day 409 and died on Day 421. On the day of hospitalization, the patient was unable to ambulate, had right sided weakness, and had ongoing confusion and aphasia and had a blood pressure of 170/92 mmHg on arrival (136/72 mmHg at the most recent study visit on Study Day 370).[8] The day before, the patient attempted to get up after dinner and had fallen. The subject had received a tetanus shot and Covid booster on Study Day 408 (also reported as Study Day 407). A head CT on Study Day 409 showed an acute left thalamic hemorrhage measuring 2.2 cm with some minimal surrounding edema. The most recent dose of study drug had been 39 days prior to the SAE of thalamus hemorrhage (14th dose of donanemab). Baseline MRI showed beginning confluence of white matter disease. No new findings from baseline were reported on the patient's last MRI in the study, which occurred on Study Day 364. A head CT the following day showed stable thalamic hemorrhage with surrounding edema and intraventricular hemorrhage layering within the posterior horns of the lateral ventricles. The hospital course included development of an upper gastrointestinal bleed and respiratory distress due to presumed aspiration event from emergent intubation and dysphagia. Although Dr. Branagan notes that a role for donanemab in the event of thalamus hemorrhage cannot be ruled out, she notes that the history of hypertension, the most common etiology of thalamus hemorrhage, is a risk factor for this event.

[8] Noted in the Applicant's response dated August 28, 2023, to an information request dated August 25, 2023.

Dr. Branagan notes that the incidence of death by person-years of exposure to donanemab in the placebo controlled portion of AACI is 18.1/1,000 person years (16/855.7 person years) and in the all donanemab pool is 13.8/1,000 person years (32/2322 person years) and does not exceed a reported incidence from Alzheimer's disease in the US of 133.8/1,000 person years[9]. This comparison is limited by comparing the population with early-stage Alzheimer's disease (mild cognitive impairment and mild dementia) with the overall Alzheimer's disease population inclusive of later stages.

Serious and Significant Adverse Events

In the placebo-controlled period of AACI, SAEs within 57 days of the last dose occurred in 16% (140/853) of donanemab-treated subjects and in 14% (124/874) of placebo-treated subjects. Similarly, in the placebo controlled pool, SAEs occurred in 16% (162/984) of donanemab treated subjects versus 14% (143/999) of placebo subjects. The findings using this approach are consistent with those using the prespecified analysis of within the treatment period plus 57 days in AACI in which SAEs occurred in 17% of donanemab-treated participants and 15% of placebo-treated participants.

The placebo-controlled pool allows for capturing of more rare events than just using AACI alone. In that pool, the most frequently reported SAEs within 57 days of the last dose (reported in at least 0.5%) and with a frequency of at least 0.2% higher in the donanemab arms compared to placebo were ARIA-E (1.5% vs 0), pneumonia (1% vs 0.3%), intestinal obstruction (0.5% vs 0%), COVID-19 (0.7% vs 0.4%), intracranial hemorrhage (0.7% vs 0.2%, driven by subdural hematoma in 0.4% vs 0%, for which Dr. Branagan did not find a role for donanemab), dehydration (0.5% vs 0.1%), pulmonary embolism (0.5% vs 0.2%), and allergic reactions/hypersensitivity (0.5% vs 0). In the all-donanemab pool, SAEs with the highest incidence were ARIA-E (1.1%), syncope (0.9%), pneumonia (0.6%), Covid-19 (0.6%), and fall (0.6%).

Dr. Branagan reviewed the SAEs of pulmonary embolism that occurred in 9 subjects in the pooled dataset, including 1 fatal case that occurred 74 days after the last dose of donanemab. Six of the 8 remaining cases, including a fatality in a patient with a past medical history of atrial fibrillation and sleep apnea (I5T-MC-AACI-(b) (6)), had risk factors for pulmonary embolism. Among the SAEs of dehydration, the subjects had confounding contributory factors. As Dr. Branagan notes, all cases of pneumonia had at least age or dementia as a risk factor.

Dr. Branagan identified SAEs of seizure in 0.4% (3/853) donanemab-treated subjects and in 0.1% (1/874) on placebo in the placebo controlled period of AACI, one of which occurred in the setting of ARIA. In the all-donanemab pool, there were 5 SAEs of seizure. SAEs of seizure either occurred in the setting of hemorrhagic stroke (I5T-MC-AACI-(b) (6)), ARIA-E (I5T-

[9] Ganguli M, Dodge HH, Shen C, Pandav RS, DeKosky ST. Alzheimer Disease and Mortality. Arch Neurol 2005; 779-784.

MC-AACI-[redacted]), did not reoccur with subsequent exposure ((I5T-MC-AACI-[redacted] I5T-MC-AACI-[redacted]), or occurred more than 200 days after the last dose (I5T-MC-AACI-[redacted]).

Dr. Branagan identified the following designated medical events, not discussed elsewhere in this memo, that in each case had risk factors for the event: ventricular fibrillation in a patient with acute myocardial infarction and a history of coronary artery disease (I5T-MC-AACI-[redacted]), acute kidney injury (I5T-MC-AACI-[redacted] I5T-MC-AACI-[redacted] I5T-MC-AACI-[redacted] I5T-MC-AACI-[redacted] I5T-MC-AACI-[redacted], I5T-MC-AACI-[redacted], I5T-MC-AACI-[redacted]), pancreatitis (I5T-MC-AACI-[redacted] I5T-MC-AACI-[redacted] I5T-MC-AACI-[redacted]), and ischemic colitis in the setting of an SAE of clostridium difficile colitis in a patient who had received ciprofloxacin with both events resolving after treatment for clostridium difficile colitis (I5T-MC-AACG-[redacted]).

ARIA, intracerebral hemorrhage, hypersensitivity and infusion related reactions, intestinal obstruction and intestinal perforation, and seizure related events will be discussed as adverse events of special interest.

In the placebo controlled period of AACI, most TEAEs were mild or moderate in severity, with approximately 12% considered severe in in the donanemab group and 9% in the placebo group. In the all-donanemab pool, approximately 10% of subjects on donanemab had a severe TEAE. The most frequent severe TEAEs in the donanemab group in the placebo controlled period of AACI were ARIA-E, ARIA H microhemorrhages, and fall, which occurred in 1.6%, 0.5%, 0.5%, respectively in donanemab and none 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 are used to manage treatment with donanemab.

Discontinuations Due to Adverse Events

In the placebo-controlled period of AACI, approximately 30% (255/853) of donanemab-treated subjects discontinued treatment compared to 20% (176/874) of placebo-treated participants. Adverse events led to treatment discontinuation in 13% of subjects on donanemab compared to 4% on placebo. Infusion-related reactions (4% for donanemab vs 0 for placebo) ARIA-E (2.5% for donanemab vs 0.3% for placebo), and ARIA-H (0.7% for donanemab vs 0.2% for placebo) were the adverse reactions that most frequently led to treatment discontinuation. These were also the most frequent events resulting in study withdrawal.

In the placebo-controlled period of AACI, 26% (226/853) of donanemab-treated participants and 20% (174/874) of placebo-treated participants withdrew from the study. Adverse events were reported to lead to study withdrawal with higher incidence in the donanemab arm compared to placebo (7.9% (67/853) versus 3.3% (29/874), respectively).

In the all-donanemab pool, approximately 6% of subjects discontinued treatment because of adverse events. Infusion related reactions (2%)and ARIA-E (1and ARIA-H microhemorrhage (0.2%) were the most frequently reported reasons for study drug discontinuation in the all-donanemab pool.

Treatment-Emergent Adverse Events (TEAEs) of All Severities

The incidence of TEAEs in the placebo controlled period of AACI was 89% in the donanemab arm and 82% in the placebo arm. The most frequently reported TEAEs in that group were ARIA-E, ARIA-H microhemorrhage, ARIA-H superficial siderosis, headache, and infusion related reaction (see Table 5). Of note, this does not include TEAEs associated with events of symptomatic ARIA.

Table 4 : Adverse Reactions Reported in at Least 5% of Subjects Treated with Donanemab and at least 2% greater than Placebo in the Placebo-controlled Period of Study AACI

Preferred Term	**Donanemab N=853 n (%)**	**Placebo N=874 n (%)**
Total Subjects with any TEAE	758 (89)	715 (82)
ARIA-H Microhemorrhage[1]	217 (25)	100 (11)
Amyloid related imaging abnormality-edema/effusion[1]	201 (24)	17 (2)
ARIA-H Superficial siderosis of central nervous system[1]	125 (15)	23 (3)
Headache	115 (13)	86 (10)
Infusion related reaction	74 (9)	4 (0.5)

Created by Dr. Branagan using the IDB ADAE dataset submitted in the 90-Day Safety Update on September 11, 2023.

[1]Events related to ARIA are based on ARIA events reported in the MRI dataset and analyzed by Senior Clinical Analyst Dr. Rui Li.

TEAEs occurred in 78% (2188/2802) in the all-donanemab pool. Dr. Branagan notes that the most frequent (at least 5%) TEAEs in that pool were ARIA-H (26%), ARIA-E (20%), COVID-19 (13%), headache (11%), fall (10%), Infusion related reaction (8%), and superficial siderosis (5%). The incidence of falls is within the reported rate of 29% for adults at least 65 years old in the general population reporting at least 1 fall in the previous year. [10]

Laboratory Findings

Dr. Branagan did not identify a safety signal for the placebo-controlled pool in mean change from baseline or shifts to high and shifts to low or in CTCAE shifts to higher grades for

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

laboratory parameters in the placebo-controlled pool or in the all donanemab pool. She found slight imbalances in TEAEs related to hyponatremia, hypercholesterolemia, and hyperglycemia in the placebo-controlled pool, although no TEAE was greater than 1.6% and the differences from placebo were not greater than 1%.

Dr. Branagan notes subject I5T-MC-AACI-(b) (6) who developed increased transaminases (ALT 4X ULN, AST > 3X ULN) and total bilirubin (2.5X ULN) with concurrent increased alkaline phosphatase (2.2X ULN), and GGT > 10X ULN that occurred 1 month after the 7th dose on Day 371. There we no further doses given. Values returned to < 2X ULN by day 400 and returned to baseline by Day 574. Dr. Branagan notes that the ratio of ALT/Alkaline phosphatase was < 2, suggesting cholestatic liver injury. She notes use of alcohol, and a history of cholelithiasis 10 years prior, at which time the subject underwent cholecystectomy. Concomitant medications included sildenafil for which hepatic injury, including cholestatic injury, has been reported, although rarely. A role for donanemab is unknown in this case. Dr. Branagan notes that alkaline phosphatase elevations to at least two times the upper limit of normal were increased in donanemab-treated subjects compared to placebo in the placebo-controlled pool; however, the overall difference was small (0.6% versus 0.2%, respectively). In the all-donanemab pool, she identified 12 subjects in addition to the subject described above with alkaline phosphatase levels at least 2x the upper limit of normal, but did not establish a role for donanemab in those cases.

Vital Signs

Dr. Branagan did not identify a safety signal in the placebo-controlled pool for vital signs, shift analyses for vital signs, or TEAEs related to vital signs. Findings in the all donanemab pool were generally similar to those in the placebo-controlled pool.

ECG/QT

Dr. Branagan did not identify a safety signal in the placebo-controlled pool for clinically meaningful changes in ECG parameters. She did not find an imbalance in frequencies of TEAEs related to ECG abnormalities overall in the placebo-controlled pool and could not establish a role for donanemab in 3 SAEs of sinus node dysfunction that occurred in patients with risk factors. She did not identify a safety signal for QT prolongation. In accordance with ICH E14 guidelines for monoclonal antibodies, a thorough QT study was not conducted.

Subgroup Analyses

In the placebo-controlled period of AACI, the incidence of ARIA-E and ARIA-H were similar between males and females. The other most common TEAEs of infusion-related reactions, superficial siderosis, and headache were similar between males and females with no difference greater than 3%, although the number of events is limited. Incidence of the most common TEAEs were similar across age groups of < 65, ≥65 - <75, and ≥75 years old (no difference greater than 4%), although the findings are limited by the relatively small numbers

of subjects in the < 65 year old group that represented approximately 10% of the study subjects. The numbers of subjects of race other than White, ethnicity other than "Non-Hispanic or Latino" or in regions other than North America or Europe were too few to make comparisons by race or by region. The incidence of common TEAEs were similar in North America and Europe were similar (no difference greater than 4%). Dr. Branagan shows that ARIA-E and headache were reported with higher frequency in patients with the lowest BMI (ARIA-E difference of 8%, headache difference of 5% in < 24.5 kg/m2 ≥27.5 kg/m2).

Other Events of Interest

Amyloid-Relating Imaging Abnormalities (ARIA)

Monoclonal antibodies directed against aggregated forms of beta amyloid, including donanemab, can cause amyloid related imaging abnormalities (ARIA) characterized as ARIA with edema (ARIA-E), which can be observed on MRI as brain edema or sulcal effusions, and ARIA with hemosiderin deposition (ARIA-H), which includes microhemorrhage and superficial siderosis. ARIA-E or ARIA-H may occur in isolation or concurrently. ARIA-H frequently occurs in association with an occurrence of ARIA-E. Current management of ARIA is not based on such relationships.

Incidence

The following discussion refers to data the placebo-controlled period of AACI unless otherwise indicated.

Table 6, extracted from Dr. Branagan's review, shows the incidence of ARIA events on treatment or within 57 days of a dose of donanemab, and the incidence of intracerebral hemorrhage on treatment or within 57 days of a dose of donanemab in the placebo-controlled portion of AACI. Similar frequencies of ARIA-E, ARIA-H, and cerebral hemorrhage > 1 cm were observed in the all-donanemab pool as observed in AACI.

Table 5 : Incidence of Treatment Emergent ARIA or Cerebral Hemorrhage in AACI

	Placebo N=874 n (%)	**Donanemab N=853 n (%)**
ARIA	122 (14)	307 (36)
ARIA-E	17 (2)	201 (24)
Symptomatic ARIA-E*	0	52 (6)
ARIA-H Isolated ARIA-H	111 (13) 105 (12)	263 (31) 106 (12)

ARIA-H microhemorrhage	100 (11)	217 (25)
ARIA-H superficial siderosis	23 (3)	125 (15)
Intracerebral Hemorrhage > 1 cm	2 (0.2)	4 (0.5)

*Symptoms of ARIA-H were not collected in Study AACI.

Most ARIA-E was co-occurring with ARIA-H; the incidence of isolated ARIA-E (i.e., incidence of ARIA-E in subjects who did not have ARIA-H at the same time on any given MRI) was 5% (44/853) on donanemab and 1% (11/874) on placebo. There was no imbalance in isolated ARIA-H between donanemab and placebo in AACI. Among new donanemab exposures in the all donanemab pool (n=1818), the incidences of ARIA (30%), ARIA-E (19%), and ARIA-H (25%) were similar to the incidence in AACI. In the all-donanemab pool (n=2802), the incidence of ARIA overall (32%), ARIA-E (20%), and ARIA-H (26%) was also similar to that in AACI alone.

As noted in Dr. Branagan's review, the Applicant identified the presence of 2-4 microhemorrhages at baseline or the presence of 1 area of superficial siderosis at baseline, as well as the number of ApoE ε4 alleles, as risk factors for ARIA-E and for ARIA-H.

Cerebral Hemorrhage

Dr. Branagan finds that intracerebral hemorrhage greater than 1 cm occurring within 57 days after the last dose of study drug was reported in 0.5% (4/853) of subjects on donanemab[11] and in 0.2% (2/874) subjects on placebo in the placebo controlled period of AACI. All 4 subjects on donanemab had risk factors for cerebral hemorrhage including an ApoE ε4 allele in 3 of the subjects and findings consistent with cerebral amyloid angiopathy including superficial siderosis prior to the event.[12]

Four additional subjects with cerebral hemorrhage greater than 1 cm in the all donanemab pool also had risk factors including thrombolytic therapy in 1 subject, and superficial siderosis and/or an ApoE ε4 allele in the other three subjects. The incidence of cerebral hemorrhage > 1 cm in the all donanemab pool was 0.3% (8 out of 2802)[13]. One additional subject (I5T-MC-

[11] I5T-MC-AACI-(b) (6) I5T-MC-AACI-(b) (6), and I5T-MC-AACI-(b) (6) and I5T-MC-AACI-(b) (6)

[12] Subject I5T-MC-AACI-(b) (6) had superficial siderosis on MRI at baseline, and elevated blood pressure at the time of the event and on 2 previous visits. Subject I5T-MC-AACI-(b) (6) with cerebral hemorrhage on day 192, had a finding of superficial siderosis beginning on day 74 in the same area as the cerebral hemorrhage and continuing at the time of the event on Day 192, and was on the antiplatelet drug prasugrel for carotid artery stenosis. Subject I5T-MC-AACI-(b) (6) with left parietal cerebral hemorrhage had a past medical history of hypertension but with blood pressure noted as normal throughout the study, and with ARIA E in left parietal, frontal, temporal lobes; 3 microhemorrhages; superficial siderosis in right frontal at the time of the event. Subject I5T-MC-AACI-(b) (6) with aspirin use prior to the event, had baseline superficial siderosis and presence of white matter disease with beginning of confluence of lesions.

[13] I5T-MC-AACI-(b) (6) I5T-MC-AACI-(b) (6) I5T-MC-AACI-(b) (6) I5T-MC-AACI-(b) (6) I5T-MC-AACI-(b) (6) and I5T-MC-AACI-(b) (6), I5T-MC-AACI-(b) (6) and I5T-MC-AACI-(b) (6)

AACI-[redacted]), homozygous for ApoE ε4, on aspirin 325 mg daily, had cerebral hemorrhage 78 days after the only dose (Day 625, 78 days after the dose and another on Day 703) in the setting of severe ARIA E (Day 569, 22 days after the only dose), ARIA H microhemorrhage and superficial siderosis. Use of anticoagulants was too limited to determine whether concomitant use is associated with an increased risk as discussed in a presentation of antithrombotic use, below.

ApoE ε4 Genotype

ApoE ε4 homozygotes have been previously shown to have an increased incidence of ARIA compared to heterozygotes and noncarriers in subjects taking monoclonal antibodies directed against aggregated forms of beta amyloid. In the placebo-controlled portion of AACI, 17 % (143/853) of subjects in the donanemab group were ApoE ε4 homozygotes, 53% (452/853) were heterozygotes, 30% (255/853) were noncarriers, and in 3 subjects genotype was unknown. In AACI, the incidence of ARIA was higher in ApoE ε4 homozygotes than in heterozygotes or in noncarriers as shown in Table 7 below.

Table 6: Incidence of ARIA and Cerebral Hemorrhage greater than 1 cm by ApoE ε4 Genotype in Subjects Exposed to Donanemab in AACI (MRI dataset)

	Non-Carriers		**Heterozygote**		**Homozygote**	
	Placebo N=250 n(%)	**Donanemab N=255 n(%)**	**Placebo N=474 n(%)**	**Donanemab (N=452) n(%)**	**Placebo N=146 n(%)**	**Donanemab N=143 n(%)**
ARIA	29 (12)	63 (25)	60 (13)	164 (36)	32 (22)	79 (55)
ARIA-E	2 (0.8)	40 (16)	9 (2)	102 (23)	5 (3)	58 (41)
ARIA-H	27 (11)	48 (19)	54 (11)	142 (31)	30 (20)	72 (50)
Cerebral Hemorrhage > 1cm	0	1 (0.4)	1 (0.2)*	3 (0.7)	0	0

*Placebo subject 5T-MC-AACI-[redacted]; Placebo subject I5T-MC-AACI-[redacted] ApoE genotype unknown

Dr. Branagan shows that among subjects treated with donanemab in the placebo-controlled period of AACI, symptomatic ARIA-E occurred in 8% of ApoE ε4 homozygotes, 7% of heterozygotes, and 4% of noncarriers.

Serious events of ARIA occurred in approximately 3% of ApoE ε4 homozygotes, approximately 2% of heterozygotes and approximately 1% of noncarriers treated with donanemab. Among subjects treated with donanemab who had ARIA-E, severe radiographic ARIA-E was greatest in ApoE ε4 homozygotes (3% (4/143) compared to heterozygotes (2%, 9/452) or noncarriers (0.4%, 1/255). Among subjects treated with donanemab who had

ARIA-H, severe radiographic ARIA-H was greatest in ApoE ε4 homozygotes (22%, 31/143) compared to heterozygotes (8%, 38/452) or noncarriers (4%, 9/255).

APOE ε4 has been associated with increased risk of intracerebral hemorrhage.[14] As Dr. Branagan notes, interpretation of these data with respect to the risk of cerebral hemorrhage in ApoE ε4 carriers on donanemab is limited because of the small numbers of cerebral hemorrhages, concomitant use of aspirin or antithrombotics in 2 subjects, and presence of findings suggestive of cerebral amyloid angiopathy, a risk factor for cerebral hemorrhage, in all 4 subjects with cerebral hemorrhage > 1 cm on donanemab in the placebo controlled portion of AACI. The placebo-treated subjects also had baseline risk factors for cerebral hemorrhage that included a known ApoE ε4 allele and baseline microhemorrhages in one of the subjects and baseline superficial siderosis in the other. The limited data do not allow for a conclusion about the risk of intracerebral hemorrhage in ApoE ε4 carriers on donanemab.

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

Symptoms

The majority of ARIA cases in AACI and overall in the placebo-controlled pool were asymptomatic, consistent with other drugs in this class. In AACI, the incidence of symptomatic ARIA-E was 6% (52/853) in subjects treated with donanemab compared to none in the placebo group. Of the 52 donanemab-treated subjects with symptomatic ARIA, 23% (12/52) were ApoE ε4 homozygotes, 57% (30/52) were heterozygotes, and 20% (10/52) were noncarriers.

The most common symptoms of ARIA-E in donanemab-treated subjects in AACI were headache (2.8%, 224/853) and confusional state (1.5%, 13/853); other reported symptoms included seizure occurring in 0.6% of donanemab-treated subjects, dizziness and nausea, each occurring in 0.5%, and fatigue, gait disturbance, and tremor each occurring in 0.4%. These symptoms are consistent with symptoms reported for this class of drugs.

In the placebo-controlled period of AACI, ARIA-E symptom severity was mild in in 3.5% (30/853), moderate in 1.4% (12/853), and severe in 1.2% (10/853) of donanemab-treated subjects. Symptomatic ARIA was not categorized by seriousness in the database.

Clinical symptoms resolved in approximately 85% (44/52) of subjects with ARIA-E in AACI, within the period of observation.

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

The incidence of symptomatic ARIA-E (4.5%) in the all-donanemab pool was similar to that observed in AACI.

Seizures, including status epilepticus, have been associated with ARIA after administration of monoclonal antibodies directed against aggregated forms of beta amyloid as noted in the approved labeling for lecanemab and for aducanumab. In addition, patients with Alzheimer's disease may be at increased risk for seizures.[15] In AACI, seizures occurring in the setting of ARIA-E occurred in 0.6% (5/853) subjects on donanemab and none (0/874) subjects on placebo. In the all-donanemab pool, seizure as a symptom of ARIA-E was reported in 0.2% of donanemab-treated subjects. Seizures, including those related to ARIA-E and ARIA-H, will be discussed later in this document.

Radiographic Severity

Among the 853 subjects treated with donanemab in AACI, the maximum radiographic severity for ARIA-E was mild in 7%, moderate in 15%, and severe in approximately 2%. The maximum radiographic severity for ARIA-H microhemorrhage was mild in 17%, moderate in 4%, and severe in 5%. The maximum radiographic severity for superficial siderosis was mild in 6%, moderate in 4%, and severe in 5%. Dr. Branagan notes similar findings for maximum radiographic severity in the all donanemab pool.

Timing of ARIA Events

Routine Safety MRIs to monitor for ARIA were to be performed to prior to the 2nd, 4th, 7th, and 14th doses and approximately 4 weeks post the last dose in AACI.

Table 8, extracted from Dr. Branagan's review, shows the timing of first ARIA-E events in the donanemab group in AACI.

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

Table 7 Timing of first ARIA-E events in Donanemab-treated Subjects in AACI

Number of Doses Prior to ARIA-E	Number of subjects experiencing a first ARIA-E	Cumulative frequency of first ARIA-E N (%)
1	8	8 (4)
2	18	26 (13)
3	90	116 (58)
4	6	122 (61)
5	8	130 (65)
6	49	179 (89)
7	9	188 (94)
10	1	189 (94)
11	1	190 (94)
13	10	200 (99)
19	1	201 (100)

Dr. Branagan finds that in AACI, approximately 58% of ARIA-E radiographic events occurred prior to the 4th dose. Eighty-nine percent occurred prior to the 7th dose. Dr. Branagan shows that in AACI, additional ARIA-E events continued to occur as late as after the 19th dose. She notes that similar timing was observed in the all-donanemab pool. First events of ARIA-H occurred with similar timing: Approximately 41% prior to the 4th dose, approximately 71% prior to the 7^{th} dose, and 93% prior to the 14^{th} dose, with additional events as late as after the 19^{th} dose.

In AACI, a first event of ARIA-E in subjects on donanemab resolved by the 12th week after detection in 63% (126/201) of subjects, by the 20^{th} week in 80% (160/201), and in 83% by the end of the study; median time to resolution was 57 days (15-287 days). Dr. Branagan notes that time to resolution in the all donanemab pool was similar to that observed in AACI.

In AACI, approximately 24% (48/201) of subjects with ARIA-E on donanemab had more than 1 treatment-emergent event of ARIA E. Thirty-five subjects (17%) had 2 events, and 13 subjects (6.5%) had more than 2 events. Although there is experience in subjects having more than 1 episode of ARIA, the data are too limited to make generalizable recommendations regarding implications or outcomes of recurrent ARIA.

The clinical studies allowed for interruption of dosing for ARIA-E or ARIA-H deemed clinically significant by the investigator. In AACI, 17% of patients (144/853) had treatment interrupted because of ARIA-E (72% of subjects with ARIA-E). There is limited experience with donanemab in continued dosing through symptomatic, radiographically mild ARIA-E that will be allowed for in the labeling, consistent with the current class approach to dosing.

Antithrombotic Use

Dr. Branagan notes that in Study AACI, antithrombotic use was allowed. The protocol excluded patients with more than 4 microhemorrhages, more than 1 area of superficial

siderosis, any macrohemorrhage (size not defined), or severe white matter disease at screening.

In AACI, subjects who received donanemab and an antithrombotic (aspirin, other antiplatelet, or anticoagulation) within 30 days prior to an event of ARIA-H had an incidence of ARIA-H of 30% (106/349) compared to subjects who received no antithrombotic (29%, 148/504). Dr. Branagan finds no difference in incidence of ARIA-H in subjects with concomitant use of anticoagulant or aspirin at least 81 mg daily or a combination compared to those using less than 81 mg aspirin daily. However, definitive conclusions about the risk of ARIA are limited by the small numbers of events and by the small numbers of subjects exposed to antithrombotic medication other than low dose aspirin.

Antithrombotic use and cerebral hemorrhage in donanemab-treated subjects and in placebo-treated subjects is shown in Table 9, extracted from Dr. Branagan's review. The number of events and the limited exposure to non-aspirin antithrombotic medications limit definitive conclusions about the risk of ARIA or intracerebral hemorrhage in patients taking antithrombotic medications.

Table 8: Antithrombotic Use and Risk of Cerebral Hemorrhage > 1 cm in AACI

	Cerebral Hemorrhage	
	Placebo n/N (%)	**Donanemab n/N (%)**
Not on antithrombotic	2/513 (0.4%)	2/504 (0.4)
On antithrombotic[a]	0/361	2/349 (0.6%)

[a]Subjects are included as having antithrombotic use if they had an event 1) while on an antithrombotic or 2) used an antithrombotic within 30 days prior to the event.

Among donanemab-treated subjects, the majority of exposures to antithrombotic medications in AACI were to aspirin < 81 mg (59%, 206/349). Approximately 10% of donanemab-treated subjects were exposed to anticoagulation. The small number of cerebral hemorrhages and small numbers exposed to antithrombotics and anticoagulants limit interpretation of these results regarding intracerebral hemorrhage in patients exposed to donanemab. In addition, confounding factors such as a history of hypertension, the presence of an ApoE ε4 allele in three donanemab-treated subjects, a history of superficial siderosis, the presence of microhemorrhages, and possible cerebral amyloid angiopathy, all risk factors for intracerebral hemorrhage, further limit definitive conclusions about the role of donanemab or concomitant use of antithrombotic medication. However, because intracerebral hemorrhages greater than 1 cm in diameter have been observed in subjects taking donanemab, class labeling will be used, recommending 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 donanemab.

As previously noted, 1 cerebral hemorrhage occurred after thrombolytic use (tenecteplase) for symptoms mimicking stroke in the setting of ARIA-E (cerebral hemorrhage, I5T-MC-AACI-[redacted]). The contribution of donanemab to the event in this case is unknown. It is important for physicians to recognize that a patient has been exposed to donanemab when presenting with stroke-like symptoms.

Approach to the Management of ARIA

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

Recommendations for dosing interruptions for ARIA events are shown in Table 11 and Table 12, as currently provided for in class labeling.

Table 11: Dosing Recommendations for Subjects with ARIA-E

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

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

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

Table 12: Dosing Recommendations for Subjects with ARIA-H

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

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

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

The labeling will recommend a recent MRI prior to initiating treatment and prior to the 2nd, 3rd, 4th, and 7th infusions. Labeling will also recommend that clinical evaluation should be performed, including MRI, if a patient experiences symptoms suggestive of ARIA. This approach is applied to the class and supported by the data in the present submission.

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

Seizures

Seizures occurred both independent of ARIA as well as in the setting of ARIA. In the placebo controlled period of AACI, the incidence of having a seizure was 1.2% (10/853) in subjects on donanemab and 0.3% (3/874) on placebo. Five of those seizures on donanemab (0.6%, 5/853) and none on placebo occurred in association with ARIA-E. In the all donanemab pool, seizure was reported in 0.7% (19/2802) overall; 6 of those seizures were reported as a symptom of ARIA-E (0.2%, 6/2802).

SAEs of seizure occurred in 0.4% in donanemab vs 0.1% in placebo in the placebo-controlled

period of AACI. Overall in the all-donanemab pool, Dr. Branagan identified 7 SAEs (0.2%, 7/2802) related to seizure on treatment or within 57 days after a dose. SAEs of seizure occurred in the setting of hemorrhagic stroke (I5T-MC-AACI-(b) (6)), ARIA-E (I5T-MC-AACI-(b) (6) also with a total of 23 microhemorrhages as well as superficial siderosis, I5T-MC-AACI-(b) (6)), did not reoccur with subsequent exposure ((I5T-MC-AACI-(b) (6) I5T-MC-AACI-(b) (6)), occurred more than 200 days after the last dose (I5T-MC-AACI-(b) (6) (b) (6)), or occurred in the setting of diabetic ketoacidosis (I5T-MC-AACI-(b) (6) metabolic encephalopathy/Covid infection.

Infusion Reactions and Hypersensitivity Reactions

In the placebo-controlled period of AACI, 9% (74/853) of donanemab subjects vs 0.5% (4/874) of placebo subjects had at least 1 TEAE of infusion-related reaction. The clinical severity of infusion-related reactions on donanemab was mild in 57%, moderate in 39%, and severe in 4%. One subject (0.1%) had an infusion reaction categorized as a SAE after administration of donanemab. In AACI, the majority (70%, 52/74) of infusion reactions occurred within the first 4 infusions of donanemab. Infusion-related reactions led to treatment discontinuation in 4% (31/853) of donanemab-treated subjects and none on placebo.

Overall, in the all donanemab pool, approximately 9% (266/2802) of subjects on donanemab had an infusion-related reaction. Sixty-eight percent (181/266) of subjects who had an infusion-related reaction on donanemab received subsequent infusions. Twenty-three percent (42/181) of those subjects received prophylactic medication with the subsequent infusion; prophylactic medications included antihistamines, acetaminophen, and corticosteroids. The incidence of subsequent infusion-related reactions after a first event on donanemab was similar with (38 %, 16/42) and without (41%, 57/139) preventative medication. Similarly, the incidence of subsequent infusion-related reactions was no different when infusions were slowed or not.

Symptoms associated with infusion reactions in AACI included chills, erythema, nausea/vomiting, dyspnea, sweating, elevated blood pressure, headache, chest pain, and low blood pressure. Dr. Branagan notes 3 cases of increases in blood pressure in the setting of infusion reactions in AACI: myocardial infarction in subject I5T-MC-AACI-(b) (6) with blood pressure of 217/117 mmHg within 5 minutes of starting the infusion (prior to the infusion was 150/80 mm Hg) in a patient with a history of hypertension and hyperlipidemia; angina with blood pressure of 168/108 mm Hg (vs 139/78 mmHg pre-dose) in subject I5T-MC-AACI-(b) (6) with past medical history of coronary artery disease and hypertension; and respiratory distress with blood pressure of 142/90 mm Hg, heart rate 118 bpm, and oxygen saturation of 82% (vs predose blood pressure of 122/76 mm Hg; heart rate 79 bpm) in subject I5T-AACI-(b) (6) with no known risk factors.

Hypersensitivity events other than infusion-related reactions occurred in approximately 3% of donanemab-treated subjects and 0.7% of placebo-treated subjects in the placebo-controlled period of AACI. In AACI, Dr. Branagan notes anaphylactic reaction in 0.4% (3/853) subjects on

donanemab and none in placebo. Angioedema was reported in 1.2% of donanemab-treated subjects vs 0.5% on placebo.

Intestinal Obstruction or Intestinal Perforation

Dr. Branagan identified an imbalance of TEAEs related to intestinal obstruction or intestinal perforation in the donanemab arm (0.7%, 6/853) compared to placebo (0.1%, 1/874) in AACI. All of the TEAEs were serious. The TEAEs of intestinal perforation occurred in 0.2% (2/853) of patients on donanemab in AACI and included intestinal perforation and large intestine perforation compared to 0.1% (1/874) in placebo that was a small intestinal perforation. The obstructions and perforations in the donanemab group were confounded by risk factors[16] in one subject who had a past medical history of small intestinal ulcer and concomitant use of Seroquel that has a warning for constipation and intestinal obstruction, and in one subject with associated with diverticulitis with sepsis who was also taking multiple medications for which labeling has intestinal obstruction listed as adverse events. The incidence of the TEAEs of Intestinal Obstruction was 0.4% (3/853) for donanemab and none in the placebo group. There was no increased incidence of constipation. In the all donanemab pool, 0.2% (5/2802) reported a TEAE of intestinal obstruction and 0.2% (5/2802) reported a TEAE of perforation. As shown in Dr. Branagan's review, the 3 SAEs of intestinal obstruction in AACI were confounded by incarcerated ventral hernia, diverticulosis, abdominal adhesions that are risk factors for intestinal obstruction[17], a history of abdominal surgery, or concomitant use of anticholinergic medication. However, a role for donanemab cannot be ruled out, including a role in exacerbating an underlying risk, given the imbalance in intestinal obstruction for donanemab compared to placebo and an incidence of 0.5% that, while within a global range reported for individuals 65 to less than 85 years of age of approximately 0.3% to 0.75%[18], exceeds the approximately 0.2 to 0.3% incidence in the placebo population of other clinical trials in an Alzheimer's disease population.[19]

Safety Profile in Patients with No or Very Low Tau Burden

Subjects with no or very low tau burden, as assessed by PET, although included in the Safety Addendum AACI, were excluded from the placebo-controlled period of AACI that included patients with low/medium or high tau burden. Dr. Branagan shows that the donanemab-treated no/very low tau subjects in the Safety Addendum (n=250) did not have a higher

[16] Hafner J, Tuma F, Hoilat GJ, et al. Intestinal Perforation. [Updated 2023 Aug 8]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK538191/

[17] Smith DA, Kashyap S, Nehring SM. Bowel Obstruction. [Updated 2023 Jul 31]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK441975/

[18] Noted in the applicant's response dated January 9, 2024, citing Long D, Mao C, Liu Y, et al. Global, regional, and national burden of intestinal obstruction from 1990 to 2019: an analysis from the Global Burden of Disease Study 2019, Int J Colorectal Dis. 2023; 38:245. https://doi.org/10/1007/s00384-023-04552-6.

[19] Noted in the Applicants's response dated January 9, 2024, citing clinical trials NCT01900665 (solanezumab) and NCT 00676143 (bapineuzumab).

incidence of deaths, SAEs, TEAEs, or ARIA compared to the donanemab-treated subjects in the placebo-controlled period of AACI (n=853). As Dr. Branagan notes, these findings are limited by the relatively small population with no/very low tau burden.

Suicidal behavior/ideation

Dr. Branagan did not identify a signal for suicide-related events.

Abuse Potential

Dr. Branagan did not identify a signal for drug abuse potential, withdrawal or rebound.

Immunogenicity

In the placebo-controlled period of AACI, Dr. Branagan notes that 88% (691/792) of donanemab-treated subjects who were evaluable for treatment emergent antidrug antibody (ADA) responses had a positive postbaseline treatment emergent ADA status compared to approximately 6% (48/821) on placebo, and all of those donanemab-treated subjects also had neutralizing antibodies present. Similar findings were observed in the placebo-controlled pool and in the all-donanemab pool. Dr. Branagan notes that the frequency of infusion-related reactions was higher in the donanemab-treated subjects with treatment emergent ADA positive status compared to those with negative status in the placebo controlled period of AACI (approximately 10% vs 2%).

Carcinogenicity

Dr. Branagan did not find an imbalance in the incidence of neoplasms between donanemab (7%, 69/984) and placebo 7.5%, 75/999) in the placebo-controlled pool. There were no individual neoplasms in which the rate for donanemab was more than 0.4% greater than in placebo. In the all-donanemab pool, the incidence of neoplasms was 4.9% (138/2802). The median duration of exposure of approximately 17 months (3 days to 950 days) in the all-donanemab pool may not be sufficient to fully characterize the carcinogenic potential in humans.

Human Reproduction and Pregnancy

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

Safety Summary

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

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

We agree with Dr. Carla Darling, Office of Medication Error Prevention and Risk Management, that a Risk Evaluation and Mitigation Strategy (REMS) is not necessary to ensure the benefits of donanemab outweigh its risks. Labeling, including a boxed warning will be used to communicate the risk of ARIA.

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

Risk of ARIA may be greater in patients with underlying cerebral amyloid angiopathy (CAA) or more severe CAA. In AACI, patients with MRI findings consistent with CAA (prior intracerebral hemorrhage greater than 1 cm in diameter, more than 4 microhemorrhages, more than 1 area of superficial siderosis, vasogenic edema, and severe white matter disease) were excluded from enrollment (as were patients with other lesions such as aneurysm or vascular malformation that could increase the risk of intracerebral hemorrhage). However, there is a high background rate of CAA in AD and many individuals with CAA do not have the characteristic findings on MRI. This makes identification of patients with CAA difficult and limits the ability to make specific recommendations to mitigate any increased risk of ARIA, if CAA does pose an increased risk. There are individuals with findings associated with CAA who have had serious outcomes during treatment with donanemab; however, given the high background rate of CAA, there are also many individuals who likely have CAA pathology who have received treatment with donanemab and have not experienced significant adverse events. Class labeling language does list risk factors for intracerebral hemorrhage. The labeling language, consistent with the class language, states that caution should be exercised when considering the use of donanemab in patients with these risk factors, and in particular for patients who need to be on anticoagulant therapy or patients with findings on MRI suggestive of CAA.

Because ARIA-E can cause focal neurologic deficits that can mimic an ischemic stroke, labeling language will also note that treating clinicians should consider whether such symptoms could be due to ARIA-E before giving thrombolytic therapy in a patient being treated with donanemab, and that patients who develop such symptoms may require a more extensive

evaluation and MRI to assess the etiology of the symptoms. Consideration should be given as to the potential benefits and risks when considering use of a thrombolytic agent in a donanemab-treated patient with symptoms of ischemic stroke. Labeling will recommend that patients carry information that identifies them as users of donanemab, and that indicates donanemab may cause ARIA that may present with symptoms mimicking ischemic stroke.

The Applicant stated in the submission that they will create a comprehensive medical education plan to ensure that the risk management strategies from the clinical trial are widely available and understood for health care professionals and that risks of ARIA are appropriately communicated to patients. This will include education for prescribing clinicians, radiologists, and other healthcare professionals to identify, monitor, and treat ARIA, to aid healthcare professions in appropriate patient selections, and to inform patients and caregivers about ARIA risks and clinical manifestations. The Applicant has additional plans for educational materials regarding infusion-related reactions. The Applicant intends to provide a card for patients noting that focal neurologic symptoms of ARIA can be similar to symptoms of stroke, and that providers should be aware that the patient is taking donanemab.[20]

8. Advisory Committee

A Peripheral and Central Nervous System Drugs Advisory Committee meeting was held on June 10, 2024, during which the efficacy and safety data of donanemab for the treatment of Alzheimer's disease were presented to the Committee and to discuss benefit-risk considerations.

The committee discussed whether the available data provide evidence of effectiveness of donanemab for the treatment of AD, and discussed support for effectiveness across tau PET subgroups. The committee voted unanimously, 11-0, that the available data show that donanemab is effective for the treatment of AD in the population enrolled in the clinical trials with mild cognitive impairment and mild dementia. The committee members noted the need for more information on diverse populations including African American and Hispanic populations and in patients with Down syndrome and other autosomal dominant forms of AD. Most committee members thought biomarker effects in patients enrolled in the Study AACI safety addendum supported efficacy in patients with no or very low tau. There was also general consensus that requiring tau PET in labeling would be impractical to implement and would impede access to treatment.

The committee also discussed the dosing regimen used in the clinical trials and if there were scientific and/or clinical considerations that may factor into a decision to stop or continue dosing with donanemab. The committee members agreed that the dosing regimen guided by reduction of amyloid plaque on PET imaging was an innovative component of the clinical trial

[20] March 1, 2024, response to information request.

design that could provide potential benefits for compliance and reduced burden on patients and the health care system. They also noted challenges in obtaining PET imaging to confirm amyloid reduction, both due to access issues and reimbursement. However, members were in agreement that more long-term data is needed to address questions on duration of amyloid clearance, how frequently patients would need to be monitored after stopping donanemab, when treatment should be re-initiated, and potential adverse effects of stopping and restarting therapy.

The committee discussed the overall benefit-risk assessment of donanemab for treatment of AD, including whether subgroups of patients exist for whom the benefit-risk assessment would be more or less favorable. The Committee commented on the lack of information in underrepresented groups studied, including African Americans and Hispanic Americans, patients with Down syndrome, patients with autosomal dominant Alzheimer's disease, and ApoE ε4 homozygotes. The Committee identified the need to educate patients and healthcare providers on the risks of donanemab, and ARIA specifically, including in underrepresented groups, and the need for education regarding monitoring for these risks. The Committee voted unanimously, 11-0, that the benefits outweigh the risk of donanemab in the treatment of AD in the population enrolled in the clinical trials with mild cognitive impairment and mild dementia.

9. Pediatrics

Pediatric patients were not enrolled in trials because AD does not occur in pediatric patients. The Applicant was granted a waiver for Pediatric Research Equity Act (PREA) requirements for this reason.

10. Other Relevant Regulatory Issues

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

11. Labeling

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

12. Postmarketing Recommendations

Risk Evaluation and Management Strategies (REMS)

The Agency has determined that at this time there is not a need for a REMS. Please refer to the review by Dr. Darling (June 28, 2024) from the Division of Risk Management for further details of this assessment.

Postmarketing Requirements (PMRs) and Commitments (PMCs)

PMRs will be as follows:

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

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

conduct a comparative retrospective cohort study using claims data with available medical chart review as needed or electronic health record data to assess clinical safety outcomes in a broad population of Alzheimer's disease patients treated with donanemab.

Agreed upon PMCs are as follows:

- Conduct a randomized, double-blind, controlled trial of donanemab in participants with early-stage Alzheimer's disease. All participants should receive an initial dosing regimen in which dosing is stopped based on reduction of amyloid, followed by randomization to either a maintenance dose(s) of donanemab or placebo for a period of at least 2 years. The primary efficacy endpoint will be the Clinical Dementia Rating Scale. The study should also collect biomarkers of Alzheimer's disease pathology. This trial may be conducted through cross over of participants in TRAILBLAZER-ALZ 3 upon completion of that trial.

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

13. Comments to the Applicant

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

1) We request that for Kisunla you submit all serious and non-serious domestic and/or foreign cases of cerebral hemorrhage greater than 1 centimeter in size that occur in ongoing studies or in the postmarketing setting as well as reports of any deaths in ongoing studies as 15-day "Alert reports" (described under 21 CFR 600.80(c)(1)). (c)(1)).

2) We request that you provide a narrative summary including analyses of ARIA-E, ARIA-H (specifying microhemorrhage or superficial siderosis), and incident cerebral hemorrhage greater than 1 centimeter in size; serious hypersensitivity reactions; serious infusion reactions; central nervous system vasculitis; intestinal obstruction; and intestinal perforation as part of your required periodic safety reports [e.g., periodic adverse drug experience report (PADER) required under 21 CFR 600.80(c)(2) , quarterly during the first 3 years post-approval and annually thereafter, through the 10th year following initial U.S. approval date.

Your analyses should include interval and cumulative data relative to the date of approval of Kisunla. Your analyses should provide an assessment of causality, with documentation of

indication, temporal association, duration of therapy, associated signs and symptoms, confounders, underlying risk factors, treatment given for the event, outcome, and dechallenge/rechallenge.

Your analyses should include clinical trial cases and postmarketing cases. Include line listings of the cases and FAERS reports in addition to your synthesized summary. 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 ARIA and cerebral hemorrhage greater than 1 centimeter in diameter please provide line listings that include:

- Case ID
- Whether the case was a clinical trial case, postmarketing spontaneous report, or postmarketing from a registry
- Age
- Alzheimer's disease stage
- Patient characteristics, including ApoE ε4 genotype if available
- Country where patient is treated
- Concomitant medications
- Time from first Kisunla dose to ARIA
- Listing of dates of Kisunla 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 Kisunla was held, and date that Kisunla dosing resumed
- Whether Kisunla was discontinued
- Specialty of the prescribing physician (e.g., neurologist, psychiatrist, internist)

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

/s/

RANJIT B MANI
07/01/2024 04:03:55 PM

SALLY U YASUDA
07/01/2024 04:34:30 PM

EMILY R FREILICH
07/01/2024 04:37:07 PM

TERESA J BURACCHIO
07/02/2024 11:43:45 AM

Summary Memorandum

Date	January 18, 2023
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 #	761248
Applicant	Eli Lilly and company
Date of Submission	5/18/2022
PDUFA Goal Date	1/18/2023
Proprietary Name	Kisunla
Established or Proper Name	donanemab
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)	700 mg IV dosed every 4 weeks for the first 3 doses followed by 1400 mg IV every 4 weeks thereafter, with dosing stopped when amyloid beta levels decline to a pre-specified threshold on PET imaging
Recommendation on Regulatory Action	Complete Response
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 and lecanemab are anti-amyloid beta-directed antibodies approved under the accelerated approval pathway for the treatment of Alzheimer's disease, with use specifically recommended for patients with mild cognitive impairment or mild dementia stage of disease. These approvals were based on a demonstration reduction of amyloid beta on PET imaging, a surrogate endpoint that was determined to be reasonably likely to predict clinical benefit. There remains 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.

Donanemab is an anti-amyloid beta (Aβ) monoclonal antibody directed against insoluble N-truncated pyroglutamate amyloid beta, which is present in brain amyloid plaques. 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 AACG, a multicenter, randomized, double-blind, placebo-controlled, parallel-group study in patients with early symptomatic Alzheimer's disease, consistent with the mild cognitive impairment and mild dementia stages of disease. The study included a 9-week screening period, a 76-week placebo-controlled treatment period, and

a 48-week immunogenicity and safety follow-up period. For the placebo-controlled period, patients were initially randomized to donanemab monotherapy, donanemab in combination with a BACE1 inhibitor (LY3202626), or placebo in a 1:1:1 ratio. The dosing regimen for donanemab was 700 mg IV dosed every 4 weeks for the first 3 doses followed by 1400 mg IV every 4 weeks thereafter, with dosing either reduced or stopped/switched to placebo when amyloid beta levels declined to a pre-specified threshold on PET imaging. Early in the study, the combination therapy arm of donanemab with a BACE1 inhibitor was discontinued with only 15 patients randomized to this group. The primary objective of the study was to evaluate whether donanemab decreases cognitive and/or functional decline as assessed by the integrated Alzheimer's Disease Rating Scale (iADRS), a simple linear combination of the Alzheimer's Disease Assessment Scale – 13-item Cognitive subscale (ADAS-Cog 13) and the Alzheimer's Disease Cooperative Study – instrumental Activities of Daily Living subscale (ADCS-iADL), at 76 weeks. Change from brain amyloid plaque as measured by 18F-florbetapir PET was listed as a secondary endpoint in the protocol.

Donanemab reduced brain amyloid plaque. Brain amyloid plaque showed a reduction from 107.2 Centiloids at baseline to 23.1 Centiloids at Week 76 in the donanemab treatment arm, compared to a value of 103.1 at baseline and 104.0 at Week 76 in the placebo arm. The donanemab treatment arm had a statistically significant reduction in brain amyloid plaque from baseline to Week 76 compared to the placebo arm (mean difference of -85.1 Centiloids; $p<0.001$). The primary efficacy endpoint analysis, change from baseline in iADRS at Week 76, demonstrated a statistically significant treatment effect in the donanemab treatment arm compared to placebo (3.20 [-32%], $p=0.042$). Prespecified analyses of data at Week 76 suggested reduced decline across clinical endpoints by approximately 20% to 40%.

The Agency has previously found with the accelerated approvals of aducanumab and lecanemab 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 reduction in brain Aβ plaque with donanemab was similar to levels demonstrated with aducanumab and lecanemab.

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 AACG was an adequate and well-controlled study that demonstrated clear and persuasive highly statistically significant 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. Given the robust, persuasive, and consistent effects of donanemab on an acceptable surrogate endpoint, brain Aβ plaque on PET, Study AACG can be considered a single adequate and well-controlled trial that provides

substantial evidence of effectiveness. An ongoing phase 3 study, AACI, is proposed to provide confirmatory evidence of the effectiveness of the donanamab in Alzheimer's disease. This study is anticipated to be completed in May 2023.

The safety of donanemab was characterized in a safety database with 1 year exposure that did not meet advice provided to the sponsor prior to the submission of the application. The Agency had previously stated in pre-BLA meeting minutes dated November 4, 2021, that the expectation for a BLA submission is at least "100 patients exposed to drug for ≥ 12 months, consistent with ICH E1 guidelines" to adequately characterize the safety of donanemab. If the exposure is assessed according to the protocol-based dose reductions, the sponsor argues that the exposure in Study AACG for 12 months is 97 patients. However, the exposure at the highest clinically relevant dose (participants who received 700 mg doses for the first 3 doses followed by the 1400 mg dose with no dose reduction or switch to placebo) considering the all-donanemab pool and Phase 1b Study AACD was 49 patients at 12 months. Given the importance of an adequate characterization of the safety profile of donanemab when used at its highest clinically relevant dose, the safety database is insufficient to adequately characterize the long-term safety of donanemab in the treatment of Alzheimer's disease.

Monoclonal antibodies directed against aggregated forms of beta amyloid, such as donanemab, 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 is usually asymptomatic, and when symptomatic, it is rarely serious, though serious asymptomatic (i.e., radiographic) and symptomatic cases can occur. ARIA was observed in 37% of participants treated with donanemab (49 out of 131) compared to 8% of participants on placebo (10 out of 125).

The incidence of ARIA-E was higher in apolipoprotein E ε4 (ApoE ε4) homozygotes (11 out of 25; 44%;) than in heterozygotes (21 out of 70; 30%) or in non-carriers (3 out of 36; 8%) treated with donanemab. The majority of ARIA-E radiographic events occurred within the first six doses, although ARIA can occur at any time. Of the 35 participants treated with donanemab in study AACG who had ARIA-E, the maximum radiographic severity was mild in 11, moderate in 16, and severe in 7. Resolution of radiographic findings occurred in 66 % of ARIA-E patients by 12 weeks and in 89% by 21 weeks after detection, and in all 35 patients by the end of the study. Isolated ARIA-H (i.e., ARIA-H in patients who did not also experience ARIA-E) was observed in 11% of donanemab-treated patients compared to 7% on placebo. There were no events of intracerebral hemorrhage greater than 1 cm in study AACG. In the ongoing and still blinded study AACI there was a fatal case of cerebral hemorrhage/hemorrhagic stroke, and in the all-donanemab pool there were 3 events of intracerebral hemorrhage in open label study AACI Safety Addendum in patients with risk factors but for whom a role for donanemab could not be ruled out. Symptomatic ARIA-E occurred in 14% (5 out of 35) of participants treated with donanemab who had ARIA-E compared to 1/1

placebo patient who had ARIA-E. Of these 5 participants, 1 was an ApoE ε4 homozygote, 2 were heterozygotes, and 2 were noncarriers. Symptoms in donanemab-treated participants in AACG who had ARIA included headache, mental status changes, cognitive disorder, nausea/vomiting, fatigue, confusion, and expressive aphasia. Clinical symptoms resolved in 2 of the 5 patients during the period of observation. There were no deaths due to ARIA in AACG or in the all-donanemab pool. However, there were 3 deaths associated with ARIA in the ongoing and still blinded AACI study. Patients who received donanemab and an antithrombotic medication (82% of which were aspirin, but included other antiplatelets, or anticoagulants) did not have an increased risk of ARIA-H compared to patients who received placebo and an antithrombotic medication.

Infusion-related reactions occurred in 8% of patients on donanemab versus none on placebo. Serious infusion reactions were reported in 2% of patients on donanemab. Infusion reactions were mild in 60% and moderate in 47%, and 90% occurred by the 5th dose. Most occurred within 30 minutes of the end of study drug administration. Anaphylaxis occurred in 4 patients in the all-donanemab pool, including anaphylactic shock requiring treatment with epinephrine. Increases and decreases in blood pressure and increases in heart rate have been observed in cases of infusion-related reactions.

The most common adverse drug reactions with donanemab are ARIA-E, ARIA-H microhemorrhage, ARIA-H superficial siderosis , nausea/vomiting, infusion-related reaction, urinary tract infection, diarrhea, and anxiety.

In summary, the results of Study AACG provide substantial evidence of effectiveness supporting the accelerated approval of donanemab for the treatment of Alzheimer's disease; however, a decision on approvability must also consider the adequacy of the safety database to support approval. The safety review has identified ARIA and infusion reactions as the primary risks associated with the use of donanemab. ARIA is a risk that has been observed with other anti-Aβ monoclonal antibodies. There are no safety issues identified in the current safety database that would preclude approval; however, given that there are only 49 subjects with 12-month exposures at the highest clinically relevant dosing regimen, the safety database is insufficient to adequately characterize the long-term safety of donanemab in the treatment of Alzheimer's disease. Therefore, a complete response for the application will be issued based on the inadequacy of the safety database to support the intended use.

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 and lecanemab are anti-amyloid beta-directed antibodies approved under the accelerated approval pathway for the treatment of Alzheimer's disease, with use specifically recommended for patients with mild cognitive impairment or mild dementia stage of disease. These approvals were based on a demonstration of reduction of amyloid beta on PET imaging, a surrogate endpoint that was determined to be reasonably	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
	likely to predict clinical 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 donanemab in patients at the early stages of symptomatic Alzheimer's disease was evaluated in Study AACG:
	  • Patients were randomized to receive placebo or donanemab
	  • The trial enrolled 257 patients: 131 in the donanemab arm and 126 in the placebo arm
	  • The primary endpoint was the change from baseline in iADRS. The iADRS is a simple linear combination of the ADAS-Cog 13 and ADCS-iADL. CDR-SB, ADAS-Cog 13, ADCS-iADL, and MMSE were secondary endpoints.
	  • Change from brain amyloid plaque as measured by 18F-florbetapir PET was listed as a secondary endpoint in the protocol.
	• Donanemab reduced brain amyloid plaque. Brain amyloid plaque showed a reduction from 107.2 Centiloids at baseline to 23.1 Centiloids at Week 76 in the donanemab treatment arm, compared to a value of 103.1 at baseline and 104.0 at Week 76 in the placebo arm. The donanemab treatment arm had a statistically significant reduction in brain amyloid plaque from baseline to Week 76 compared to the placebo arm (mean difference of -85.1 Centiloids; $p<0.001$).
	• The primary efficacy endpoint analysis, change from baseline in iADRS at Week 76, demonstrated a statistically significant treatment effect in the donanemab treatment arm compared to placebo (3.20 [-32%], $p=0.042$.
	• The donanemab treatment regimen demonstrated favorable numerical results on secondary clinical endpoints with nominal statistical significance for ADAS-Cog 13 at Week 76.
		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 donanemab is similar to that observed with aducanumab and lecanemab, drugs 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 donanemab on clinical endpoints in Study AACG contributed to the reasonable likelihood that a lowering of amyloid beta plaque will result in clinical benefit.
		
		Under the accelerated approval pathway, a clinical trial would be required to confirm the benefits of donanemab in AD as a post-marketing requirement (PMR). A Phase 3 study, AACI, is currently ongoing and may be suitable to meet that requirement.

Risk and Risk Management	• The safety database includes 1408 participants (1402 of the 1408 with Alzheimer's disease) who had received at least one dose of donanemab intravenously, including 827 participants with Alzheimer's disease with mild cognitive impairment or mild dementia treated for 6 months, and 49 participants treated for 12 months at the proposed dose.	The safety database patients with 12 months of exposure at the proposed dose contains only 49 patients. Given the importance of an adequate characterization of the safety profile of donanemab when used at its highest clinically relevant dose,

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• The most common TEAEs in the placebo-controlled trial that was the primary source of evidence of effectiveness (at least 5% and at least 2% greater than placebo) were related to ARIA-E (27%), ARIA-H microhemorrhage (20%), ARIA-H superficial siderosis (17%), nausea/vomiting (grouped terms, 13%), infusion related reaction (8%), urinary tract infection (10%), diarrhea (8%), and anxiety (5%) in the donanemab arm. • Less common reactions in Study AACG (at least 2% and at least 2% greater than placebo) included bronchitis/lower respiratory tract infection (grouped terms), hypotension, and bradycardia. • ARIA was observed in 37% of participants treated with donanemab, compared to 8% on placebo in Study AACG. • Clinical symptoms were present in 4% of participants treated with donanemab who had an observation of ARIA, compared to 1% on placebo. The most common symptom in patients with ARIA treated with donanemab was mental status change, occurring in one donanemab-treated participant compared to none on placebo. • ARIA-E was observed in 27% of participants treated with donanemab, compared to 1% of participants on placebo. Among participants treated with donanemab, the maximum radiographic severity was mild in 8%, moderate in 12%, and severe in 5% of participants. The majority of ARIA-E radiographic events occurred early in treatment (80% within the first six doses). After detection, resolution occurred in 66% of participants by 12 weeks, 31% by 20 weeks, and in all participants overall. The incidence of ARIA-E was higher in apolipoprotein E ε4 (ApoE ε4) homozygous carriers than in ApoE ε4 heterozygous carriers or non-carriers (44%, 30%, and 8%, respectively).	the safety database is insufficient to adequately characterize the long-term safety of donanemab in the treatment of Alzheimer's disease. A future resubmission will need to consider further characterization of the risks identified in the current safety database, including: • ARIA • Infusion-related reactions • Serious hypersensitivity reactions • Immunogenicity

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• ARIA-H in the setting of ARIA-E associated with the use of donanemab was observed in 37% of participants treated with donanemab, compared to 8% of participants on placebo. Isolated ARIA-H was observed in 11% of participants treated with donanemab, compared to 7% of participants on placebo. There were no intracerebral hemorrhages greater than 1 cm in either donanemab or placebo arms. • There was no increased risk of ARIA-H in patients who received donanemab 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 donanemab arm was 20/131 (15%) vs. 19/131 (15%) compared to 7/125 (6%) vs. 2/125 (2%) in the placebo arm. • Hypersensitivity and infusion related reactions – Serious cases of infusion related reaction were reported in 2% of participants treated with donanemab compared to none on placebo in Study AACG. Increases and decreases in blood pressure and increases in heart rate were observed in participants with infusion related reactions. Infusion related reaction was the most frequent adverse reaction reported to lead to treatment discontinuation and study withdrawal in Study AACG. Serious cases of anaphylaxis were observed in participants treated with donanemab. • Immunogenicity – Up to 92% of participants treated with donanemab developed anti-donanemab antibodies and all these participants developed neutralizing antibodies. <u>Uncertainties</u> • Patients with moderate or severe dementia were not enrolled in the key studies analyzed for the review of safety; therefore, safety outcomes for initiating therapy in these patients are unknown.	

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• Treatment with donanemab was discontinued after achieving amyloid plaque reduction criteria in the key studies analyzed for the review of safety; therefore, there is no experience with respect to safety in continuing treatment in patients who have achieved amyloid plaque reduction. • Due to the small number of participants with 12 months or more of exposure at the proposed dose, characterization of the risk profile for treatment with donanemab in this population is inadequate. • A low number of subjects were enrolled in the placebo-controlled study of AACG within the demographic subgroups of age less than 65 years, age 85 years or older, non-White race, and Hispanic ethnicity, and conclusions regarding the impact of these demographic subgroups on the frequency of adverse events cannot be drawn. • The optimal timing and frequency of MRI monitoring as a tool for mitigating ARIA is unknown. • The safety of treating participants who experienced intracerebral hemorrhage greater than 1 cm while on treatment with additional doses of donanemab 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. • Conclusions about the carcinogenic potential of donanemab cannot be drawn, given the low number of subjects with exposure to donanemab for at least 12 months or more. • Whether the risk of ARIA or cerebral hemorrhage in patients with AD treated with donanemab 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.	

2. Background

This application under review is for donanemab (previously LY3002813), proposed for the treatment of Alzheimer's disease (AD). Donanemab is a humanized, immunoglobulin gamma 1 (IgG1) monoclonal antibody administered by intravenous (IV) infusion directed against insoluble N-truncated pyroglutamate amyloid beta, which is present in brain amyloid plaques. 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. Two anti-amyloid beta-directed antibodies, aducanumab and lecanemab have been

approved under that accelerated approval pathway for the treatment of Alzheimer's disease, with use specifically recommended for patients with mild cognitive impairment or mild dementia stage of disease. These approvals were based on a demonstration of reduction of 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, anti-Aβ monoclonal antibodies, including donanemab, 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 AACG, a multicenter, randomized, double-blind, placebo-controlled, parallel-group study in patients with early symptomatic Alzheimer's disease, consistent with the mild cognitive impairment and mild dementia stages of disease. An ongoing phase 3 study, AACI, is proposed to provide confirmatory evidence of the effectiveness of the donanamab in Alzheimer's disease. This study is anticipated to be completed in May 2023.

3. Product Quality

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

The assessment of manufacturing information provided in the application concluded that the methodologies and processes used for drug substance and drug product manufacturing, release and stability testing are robust and sufficiently controlled to result in a consistent and safe product. The drug substance manufacturing process is robust for inactivation and removal of adventitious agents. No approvability issues were identified from a sterility assurance or microbiology product quality perspective.

OPQ has determined that the data submitted in this application are adequate to support the conclusion that the manufacture of KISUNLA is well-controlled and leads to a product that is pure and potent and recommends approval of Kisunla (donanemab-azbt).

OPQ has the following comment for the applicant:

Include glycosylation profiling in the release specification for donanemab drug substance using a validated testing method and establish acceptance criteria for main glycan forms, high mannose, and other afucosylated species with upper and lower limits, as applicable. Provide the results of the method validation for glycosylation profiling and the data and analysis used to set acceptance criteria.

4. Nonclinical Pharmacology/Toxicology

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

The key findings from the nonclinical review are summarized below:

Pharmacology:

- Donanemab is a humanized immunoglobulin gamma 1 (IgG1) monoclonal antibody directed against insoluble N-truncated pyroglutamate amyloid beta

Toxicology:

- Cynomolgus monkey: A 6-week (GLP-compliant) IV toxicity study (with 3-month recovery) was conducted with donanemab administered by IV injection at doses of 0, 1, 10, and 100 mg/kg QW. No drug-related findings were observed on a standard battery of safety parameters.
- PDAPP mouse: In GLP-compliant studies, a murine surrogate (mE8c) was administered by SC injection for 6 weeks at doses of 0, 10, 30, and 100 mg/kg QW or for 6 months at doses of 0, 30 and 100 mg/kg QW. No drug-related findings were observed on a standard battery of safety parameters. Toxicokinetic analysis was included in both studies but are not considered appropriate for calculation of safety margins, as these studies are only for hazard identification.

Reproductive and developmental toxicology:

- The Division agreed during clinical development that reproductive and developmental toxicology studies did not need to be conducted because of the age of the intended patient population.

Genotoxicity:

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

Carcinogenicity:

- Carcinogenicity studies were not conducted because they were not considered feasible because of the lack of pharmacologically relevant species.

Tissue Cross Reactivity:

- No relevant (non-cytoplasmic), specific staining was detected with donanemab in normal human or cynomolgus monkey tissues.

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

5. Clinical Pharmacology

An integrated Office of Clinical Pharmacology (OCP) review was written by Anantha Ram Nookala, Ph.D., Michael Bewernitz, Ph.D., Mohsen Rajabiabhari, Ph.D., Xiulian Du, Ph.D., Yow-Ming Wang, Ph.D., Atul Bhattaram, Ph.D., Bilal AbuAsal, Ph.D., Sreedharan Sabarinath, Ph.D., Hao Zhu, 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 donanemab is supported by amyloid PET reduction in the Phase 1 Study AACD, treatment-response relationships, tau PET data, and plasma biomarker (p-tau217 and GFP) data in Study AACG.
- The recommended dose is 700 mg by IV infusion every 4 weeks over (b) (4) 30 minutes for the first three doses. Subsequent doses are 1400 mg IV infusions over 30 minutes every 4 weeks.
- There is no clinical pharmacology evidence to support dose cessation after achieving a reduction in amyloid PET below a certain value or treatment duration.
- No dose adjustment is needed based on intrinsic and extrinsic factors.
- Minor differences were noted between the pivotal clinical trial (lyophilized) and to-be-marketed (solution) donanemab formulations. The applicant performed supportive studies to compare the formulations. OBP confirmed that applicant has provided adequate comparability studies to demonstrate that the to-be-marketed product and the pivotal clinical trial formulation are comparable.
- Overall, the immunogenicity database consisted of 129 subjects from Study AACG from which anti-donanemab antibody (ADA) results were available. Of these subjects, treatment-emergent ADAs (TE-ADAs) were detected in 119 subjects (92.2%). Clinical samples for potential neutralizing activity were characterized in TE-ADA positive subjects and neutralizing antibodies (Nabs) were detected in all the subjects

(119/119; 100%). All the TE-ADA subjects have developed the ADA titers by week 16 and many of the subjects (84/107; 78.5%) have achieved the individual maximum titer by week 24. The presence of TE-ADAs had an effect on various PK measures, such as Cmin,ss and AUCss. However, the changes in donanemab exposures were found not to affect amyloid PET reduction.

- As a humanized IgG1 monoclonal antibody, donanemab is expected to be degraded by proteolytic enzymes into small peptides and amino acids via catabolic pathways in the same manner as endogenous IgGs.

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 James (Hsien-Ming) Hung, Ph.D., Division Director.

The efficacy of donanemab for this application was based on an analysis of change from baseline to Week 76 in brain amyloid plaque as measured by ^{18}F-florbetapir PET and quantified by a composite standardized uptake value ratio (SUVR) in Study AACG.
Study AACG was a multicenter, randomized, double-blind, placebo-controlled, parallel group study in patients with early symptomatic Alzheimer's disease. Randomization was stratified by investigative site only. The study included a 9-week screening period, a 76-week placebo-controlled treatment period, and a 48-week safety follow-up period. For the placebo-controlled period, patients were initially randomized to donanemab monotherapy, donanemab in combination with LY3202626 (BACE1 inhibitor), or placebo in a 1:1:1 ratio. Early in the study, the combination therapy arm was discontinued with only 15 patients randomized to this group. The study did not include a long-term extension.

Study Population
Study AACG enrolled patients age 60 to 85 years who had a progressive change in memory function for at least 6 months and evidence of a mild degree of cognitive impairment on a screening cognitive assessment (CogState Brief battery learning/working memory score of 82 to 90 which was amended to a Mini-Mental State Examination (MMSE) score of 20 to 28). The protocol did not specify a formal clinical diagnosis of Alzheimer's disease, but the inclusion criteria are consistent with a diagnosis of MCI due to Alzheimer's disease or mild Alzheimer's disease dementia based on operationalized criteria from the 2018 NIA-AA Research Framework for Alzheimer's disease (Jack et al. 2018). Patients were required to have evidence of Aβ pathology by quantitative assessment on PET and evidence of a topographic tau disposition pattern consistent with Alzheimer's disease.

Patients were excluded for any neurologic condition (other than AD) contributing to cognitive impairment, or current serious or unstable illnesses including cardiovascular, hepatic, renal, gastroenterologic, respiratory, endocrinologic, psychiatric, immunologic, or hematologic

diseases. Patients were also excluded if a brain MRI performed at screening showed evidence of any of the following: ARIA-E, cerebral microhemorrhages, more than 1 area of superficial siderosis, or any macrohemorrhage (intracerebral hemorrhage greater than 1 cm) or severe white matter disease.

Clinical Endpoints

The primary endpoint was the change from baseline in the integrated Alzheimer's Disease Rating Scale (iADRS) at Week 76. The iADRS is a simple linear combination of the Alzheimer's Disease Assessment Scale – 13-item Cognitive subscale (ADAS-Cog 13) and the Alzheimer's Disease Cooperative Study – instrumental Activities of Daily Living subscale (ADCS-iADL), and its score ranges from 0 to 146 with lower scores indicating greater disease severity. The iADRS was developed to assess function and cognition in a single measure that is more sensitive to change and treatment effects in patients at the early stages of the disease (Wessels et al. 2015).

Surrogate Endpoint

Change from baseline in brain amyloid plaque as measured by 18F-florbetapir PET and quantified by a composite SUVR was assessed at Week 24, Week 52, and Week 76 and listed as a secondary endpoint in the protocol. The primary amyloid PET analysis was the SUVR calculated for a composite summary region of 6 cortical regions (anterior cingulate, posterior cingulate, medial orbital frontal, lateral temporal, lateral parietal, and precuneus) with whole cerebellum as a reference region. SUVR values were converted to the Centiloid scale (Navitsky et al. 2018) for analysis and reporting.

The Division has previously determined that a reduction in beta amyloid plaque burden measured by PET imaging is reasonably likely to predict clinical benefit. Beta amyloid plaque is an underlying, fundamental, and defining pathophysiological feature of Alzheimer's disease. Although the role of beta amyloid and its relationship to other pathophysiological features of Alzheimer's disease, such as tau and neurodegeneration, is complicated, the presence of beta 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 beta amyloid plaque, and that successfully accomplishes that reduction, has the potential to convey clinical benefit.

Dosing

IV infusions of donanemab or placebo were administered over a minimum of 30 minutes for up to 72 weeks. Patients were to receive 700 mg every 4 weeks for the first 3 doses, then 1400 mg every 4 weeks up to Week 72.

Double-blinded dose reductions of donanemab were guided by amyloid PET levels measured at Week 24 and Week 52. If the amyloid plaque level was 11 to <25 Centiloids, the dose was lowered to 700 mg at the next infusion. If the amyloid plaque level was <11 Centiloids on a single scan or 11 to <25 Centiloids on 2 consecutive scans, donanemab was switched to placebo for all subsequent administrations.

Dose modifications/discontinuations for ARIA

Dose modification criteria were established to account for the expected occurrence of ARIA-E and ARIA-H. Dose reduction or suspension were dependent on the radiographic severity of ARIA-E as detected by MRI, the presence or absence of clinical symptoms, and the severity of symptoms, if present. If a dose reduction was required, donanemab was reduced from 1400 mg to 700 mg or from 700 mg to placebo. For cases which did not call for a protocol-mandated temporary discontinuation, the investigator could have chosen to temporarily discontinue donanemab after discussion with the applicant. If a patient had a second occurrence of ARIA-E and had previously been dose reduced or temporarily discontinued from donanemab, then donanemab was permanently discontinued. Donanemab was permanently discontinued in patients with any increase in ARIA-H accompanied by clinically significant symptoms or >4 new microhemorrhages, >1 new area of superficial siderosis, or any macrohemorrhage regardless of symptoms.

Statistical Analysis Plan:

Surrogate Endpoint

Change from baseline in brain amyloid as measured by PET was analyzed with a mixed effects model with repeated measures (MMRM) with fixed effects of treatment, visit, treatment-by-visit interaction, and baseline SUVR and age at baseline as covariates.

Clinical Endpoints

Change from baseline for clinical endpoints was assessed with MMRM including the terms baseline score, pooled investigator, treatment, visit, treatment-by-visit interaction, baseline-by-visit interaction, concomitant Alzheimer's disease medication use at baseline, and age at baseline. Bretz's graphical approach was used to control the study-wise type I error rate for the primary and key secondary endpoints at an alpha level of 0.05. If the primary statistical analysis was statistically significant, analyses were to be performed on CDR-SB, ADAS-Cog 13, iADL, and MMSE to determine statistical significance for secondary endpoints.

Subgroup Analyses

Subgroup analyses for amyloid PET, iADRS, and CDR-SB were planned for the following pre-defined groups:

- ApoE ε4 carrier status (carrier or non-carrier)
- Baseline MMSE (20≤ MMSE ≤26 and MMSE ≥27)
- Tau PET level at baseline: no tau (SUVR < 1.10), low tau (1.10≤ SUVR <1.23), and medium tau (SUVR ≥1.23)

Results

A total of 1955 patients were screened for entry into the study and 272 patients continued to randomization. Table 1 contains information regarding demographic and disease characteristics for each treatment arm in the Full Analysis Set. Demographic and baseline characteristics were reasonably balanced across the treatment arms and generally

representative of the patient population except for an under-representation of African American and Hispanic patients. Overall, 91% of patients were enrolled in the United States. The mean baseline scores on the CDR-SB, MMSE, ADAS-Cog 13, and the ADCS-iADL appear to be consistent with a population with mild cognitive impairment and mild to minimal

functional impairment, although there are a few outliers who had more marked impairment on these assessments.

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

Demographic Parameters	**Placebo** (N=120) n (%)	**Donanemab** (N=125) n (%)	**Total** (N=245) n (%)
Sex			
Male	59 (49%)	61 (49%)	120 (49%)
Female	61 (51%)	64 (51%)	125 (51%)
Age			
Mean years (SD)	75.3 (5.4)	74.9 (5.5)	75.1 (5.5)
Median (years)	76	75	75
Min, max (years)	64, 85	61, 86	61, 86
Not Hispanic or Latino	117 (97.5%)	121 (97%)	238 (97%)
Laboratory ApoE ε4 Status			
Carrier	88 (73%)	92 (74%)	180 (73%)
Homozygote	26 (22%)	25 (20%)	51 (21%)
Heterozygote	62 (52%)	67 (54%)	129 (53%)
Non-carrier	31 (26%)	33 (26%)	64 (26%)
Undetermined	1 (<1%)	0	1 (<1%)
Baseline CDR-SB			
Mean (SD)	3.37 (1.70)	3.55 (2.04)	3.46 (1.88)
Median	3.5	3.5	3.5
Min, Max	0.5, 8.0	0.5, 11.0	0.5, 11.0
Baseline MMSE	115	121	236
<20	6 (5%)	9 (7%)	15 (6%)
≥20 - <27	88 (77%)	88 (73%)	176 (75%)
≥27 - ≤30	21 (18%)	24 (20%)	45 (19%)
Min, Max	16, 29	14, 29	14, 29
Concomitant AD medication			
Cholinesterase inhibitors and/or Memantine	80 (67%)	86 (69%)	166 (68%)
Cholinesterase inhibitors	71 (59%)	75 (60%)	146 (60%)
Memantine	27 (23%)	30 (24%)	57 (23%)
Region			
United States	109 (91%)	115 (92%)	224 (91%)
Rest of the World			
Canada	11 (9%)	10 (8%)	21 (9%)

Surrogate Endpoint

Donanemab treatment demonstrated a statistically significant treatment effect on the surrogate endpoint of change from baseline in brain amyloid as measured by 18F-florbetapir PET and reported as Centiloids at Week 76 (-85.1, p<0.001) (Table 2). The results indicate a

time-dependent relationship for reduction of brain amyloid with the donanemab dosing regimen which nears a plateau by Week 52 (Figure 1).

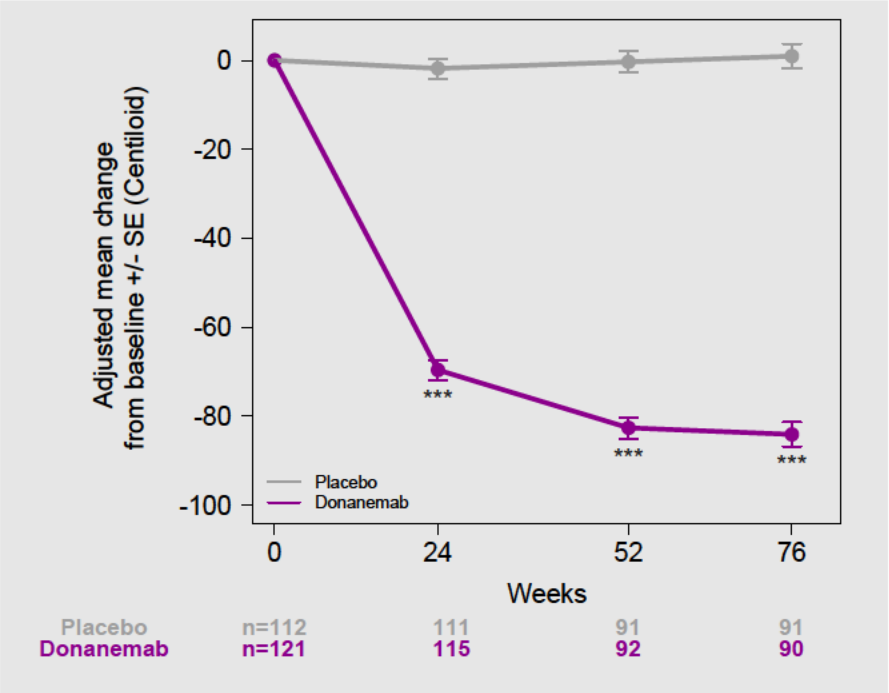
Changes in brain amyloid as measured by PET were also presented using SUVR. The change from baseline in brain amyloid at Week 76 in the donanemab arm compared to placebo was -0.46 (p<0.001). Please refer to Dr. Krudys's review for complete SUVR results.

Table 2: Study AACG Surrogate Endpoint Analysis (Centiloids)

	Placebo (N=112)	**Donanemab** (N=121)
Baseline Centiloid		
n	112	121
Mean (SD)	103.1 (33.8)	107.2 (33.9)
Min, max	38.7, 225.2	41.8, 216.2
Change from Baseline in Centiloid at Week 24		
n	111	115
Least square mean	-1.8	-69.6
Standard error	2.3	2.2
Difference from placebo		-67.8
95% CI for difference		(-74.0, -61.6)
p-value		<0.001
Change from Baseline in Centiloid at Week 52		
n	91	92
Least square mean	-0.35	-82.7
Standard error	2.4	2.4
Difference from placebo		-82.3
95% CI for difference		(-89.0, -75.6)
p-value		<0.001
Change from Baseline in Centiloid at Week 76		
n	91	90
Least square mean	0.9	-84.1
Standard error	2.7	2.7
Difference from placebo		-85.1
95% CI for difference		(-92.7, -77.4)
p-value		<0.001

Source: Table AACG.5.8 in Study AACG CSR

Figure 1: Study AACG Change from Baseline in Brain Amyloid (Centiloids)



Created by the reviewer from Table AACG.5.8 in Study AACG CSR
***p<0.001

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

Primary Endpoint

The primary efficacy endpoint analysis, change from baseline in iADRS at Week 76, demonstrated a statistically significant treatment effect in the donanemab treatment arm compared to placebo (3.20 [-32%], p=0.042) (Table 3).

Table 3: Study AACG Primary Endpoint Analysis

	Placebo (N=120)	**Donanemab** (N=125)
Baseline iADRS		
n	120	125
Mean	106.06	106.30
Change from Baseline in iADRS at Week 76		
n	91	93
Adjusted mean	-10.06	-6.86
Standard error	1.14	1.14
Difference from placebo		3.20
95% CI for difference		(0.12, 6.27)
% difference vs. placebo		-32%
p-value (compared with placebo)		0.042

Source: Table AACG.5.1 in Study AACG CSR

Secondary Clinical Endpoints

The estimate of the treatment difference between the donanemab and placebo arms for the first secondary endpoint in the hierarchy, CDR-SB at Week 76, numerically favored donanemab, but was not statistically significant (-0.36 [-23%], p=0.14) (Table 4). Favorable trends were observed across all secondary endpoints with nominal statistical significance being achieved at one or more timepoints. It does not appear that iADRS is solely driven by either component. Dr. Krudys 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.

Table 4: Study AACG Secondary Clinical Endpoint Analysis (Full Analysis Set, Week 76)

	Placebo (N=120)	**Donanemab** (N=125)
Baseline CDR-SB		
N	120	125
Mean	3.37	3.55
Change from Baseline in CDR-SB at Week 76		
N	90	93
Adjusted mean	1.58	1.22
Standard error	0.18	0.18
Difference from placebo		-0.36
95% CI for difference		(-0.83, 0.12)
% difference vs. placebo		23%
p-value (compared with placebo)		0.14
Baseline ADAS-Cog 13		
N	120	125
Mean	27.53	27.68
Change from Baseline in ADAS-Cog 13 at Week 76		
N	93	93
Adjusted mean	4.77	2.91
Standard error	0.66	0.66
Difference from placebo		-1.86
95% CI for difference		(-3.63, -0.09)
% difference vs. placebo		39%
p-value (compared with placebo)		0.040
Baseline ADCS-iADL		
N	120	125
Mean	48.58	48.98
Change from Baseline in ADCS-iADL at Week 76		
N	91	93
Adjusted mean	-5.20	-3.98
Standard error	0.74	0.74
Difference from placebo		1.21
95% CI for difference		(-0.77, 3.20)
% difference vs. placebo		23%

p-value (compared with placebo)		0.230
Baseline MMSE		
N	115	121
Mean	23.77	23.56
Change from Baseline in MMSE at Week 76		
N	90	91
Adjusted mean	-2.98	-2.35
Standard error	0.39	0.39
Difference from placebo		0.64
95% CI for difference		(-0.40, 1.67)
% difference vs. placebo		21%
p-value (compared with placebo)		0.227

Source: Tables AACG.5.2, AACG.5.3, AACG.5.4, and AACG.5.5 in Study AACG CSR
All p-values are nominal

Pharmacodynamic Endpoints

Plasma p-tau 217 was evaluated in 242 patients (119 in the placebo arm and 123 in the donanemab treatment arm). The applicant reports a decrease in plasma p-tau 217 with donanemab treatment with log10 LS mean changes at Week 76 for placebo and donanemab of 0.03 and -0.11, respectively (LS means difference of -0.14, p<0.001). There was a significant correlation between change from baseline in plasma p-tau 217 and percent change in amyloid PET from baseline (R=0.484, p<0.0001).

Plasma glial fibrillary acidic protein (GFAP) was evaluated in 210 patients (104 in the placebo arm and 106 in the donanemab treatment arm). The applicant reports a decrease in GFAP with donanemab treatment with log10 LS mean changes at Week 76 for placebo and donanemab of 0.06 and -0.06, respectively (LS means difference of -0.12, p<0.001). There was a significant correlation between change from baseline in GFAP and percent change in amyloid PET from baseline (R=0.453, p<0.0001).

Treatment effects were not observed for plasma NfL.

There was no notable treatment difference in change from baseline in hippocampus volume. Donanemab treatment was associated with a decrease in whole brain volume with LS mean changes at Week 76 for placebo and donanemab of -19.95 cm^3 and -24.53 cm^3 (LS mean difference of -4.56 cm^3, p=0.003) and an increase in total ventricular volume with LS mean changes at Week 76 for placebo and donanemab of 6.38 cm^3 and 8.66 cm^3 (LS mean difference of 2.28 cm^3, p<0.001). Given the favorable results on clinical endpoints observed in Study AACG, Dr. Krudys questions the clinical relevance of the changes to whole brain volume and total ventricular volume. Dr. Krudys also notes that plasma NfL, a marker of neurodegeneration in Study AACG, does not suggest a greater extent of neurodegeneration with donanemab treatment. See Dr. Krudys's review for additional vMRI data, including effects in other brain regions.

The primary prespecified comparisons of change from baseline to Week 76 in global tau load and annualized global tau load computed from the Tau IQ algorithm showed no treatment

differences, 0.01 (-0.01, 0.03), p=0.56 and 0.00 (-0.1, 0.02), p=0.60, respectively. Another prespecified analysis of the overall cortical tau level using a weighted neocortical composite SUVR demonstrated a treatment effect in favor of donanemab, 0.035 (0.008, 0.062), p=0.0125 or 34%. Post hoc regional analyses performed for target brain regions suggested a slowing of tau increase for the various regions.

Relationship between Amyloid PET and Clinical Endpoints

The correlation between the change from baseline on amyloid PET and the change from baseline in clinical endpoints was explored separately in the placebo and the donanemab treatment arms at the individual level. No statistically significant correlations were observed.

Using a disease progression model, a decrease in amyloid plaque was associated with a slowing in disease progression relative to placebo. Similarly, a decrease in plasma p-tau 217 was also associated with a decrease in the rate of disease progression. See the clinical pharmacology review for a detailed review of these models.

Biostatistics Review Conclusions

Dr. Massie noted that the study met the primary objective, demonstrating a statistically significant treatment effect on iADRS, but that the analysis plan did not include a pathway for multiplicity adjusted testing of brain amyloid deposition. He also notes that the correlation between change in iADRS and change in amyloid PET SUVR is small. Dr. Massie acknowledges the reduction in amyloid, 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 there is no apparent clinical endpoint treatment effect in ApoE ε4 non-carriers despite having amyloid reductions comparable to ApoE4 carriers.

Efficacy Conclusions

The applicant has submitted data to support the accelerated approval of donanemab 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, AACG, that demonstrated a robust and statistically significant treatment effect for donanemab on brain amyloid plaque as measures by PET at Week 76, compared to no change in amyloid beta in the placebo group. These findings were supported by the primary efficacy endpoint analysis, change from baseline in iADRS at Week 76, demonstrated a statistically significant treatment effect in the donanemab treatment arm compared to placebo (3.20 [-32%], p=0.042). Prespecified analyses of data at Week 76 suggested reduced decline across clinical endpoints by approximately 20% to 40%.

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 AACG on an acceptable surrogate endpoint that is reasonably likely to predict clinical benefit are robust and persuasive, and that Study AACG 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 donanemab is supported by the exposure-response relationships from Study AACG 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 AACG did not control for type I error at the 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 there is no apparent clinical endpoint treatment effect in ApoE ε4 non-carriers despite having amyloid reductions comparable to ApoE4 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.

The Agency has previously found, with the accelerated approvals of aducanumab and lecanemab, 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 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 donanemab in Study AACG support the use of the reduction of brain Aβ plaque on PET as a surrogate endpoint reasonably likely to predict clinical benefit.

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 AACG 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 the results of Study AACG provide evidence of effectiveness supporting the accelerated approval of donanemab for the treatment of Alzheimer's disease, a decision on approvability must also consider the adequacy of the safety data to support approval. Deficiencies in the safety database have been identified that will preclude approval of the drug despite evidence of effectiveness and these deficiencies are discussed further in the following section.

7. Safety

Dr. Natalie Branagan performed the safety review for the submission with CDTL, Dr. Ranjit Mani, and Deputy Director for Safety, Dr. Sally Yasuda.

Exposures and Adequacy of the Safety Database

The primary safety data are from Study AACG, a completed placebo-controlled study. The dosing regimen in AACG provided for 700 mg q 4 weeks for 3 doses followed by 1400 mg q 4 weeks for up to 72 weeks, with an allowance for reduction to 700 mg or placebo based on amyloid plaque reduction at weeks 24 or 52. Ongoing open label studies AACH Part B, AACI Safety Addendum, and AACN-Dona Cohort, with the same titration and that also include an allowance for stopping treatment based on amyloid plaque, provide supportive information and were pooled with donanemab-treated subjects from Study AACG to create an all-donanemab pool allowing for analysis of adverse events occurring in patients who have had exposure for up to 12 months. Blinded data from the placebo-controlled period of AACI were also included in the submission.

The adequacy of the safety database was discussed with the applicant as early as the EoP2 meeting for IND 109157, held on July 20, 2021. In that document, exposures for the initial submission were projected to be 72 subjects with at least 12 months of exposure to donanemab, with 97 subjects including those who switched to placebo after the 24 or 52 week amyloid scan. At the time of the planned safety update, the applicant projected there would be 107 subjects with at least 12 months of exposure to donanemab, and 144 subjects including those who switched to placebo after the 24 or 52 weeks amyloid scan. In that document as well as other communications including a March 4, 2022, email from the applicant, the applicant stated its position that a smaller database for 12 month exposures to donanemab would be acceptable because donanemab is not intended to be given chronically for an indefinite period of time, but rather is expected to be dosed for a limited duration, until amyloid plaque levels are below the positive threshold (hereafter referred to as amyloid negativity) is reached. The applicant stated that "As such, the most important contributions to understanding the known safety profile of donanemab and the therapeutic class, amyloid-related imaging abnormalities (ARIA), as well as infusion-related reactions (IRR), come from data in the first 6 months of dosing. Based on Study AACG data, it is anticipated that 25% of patients will reach amyloid negativity and no longer need continued donanemab dosing by 6 months…". The applicant projected that it would have more than 600 patients treated for at least 6 months by the safety update.

The meeting minutes from the August 26, 2021, pre-BLA meeting refer to the July 20, 2021 meeting stating that, as discussed at that meeting, an adequate characterization of the safety profile of donanemab needs to be provided with the initial BLA submission. The Agency stated that it did not agree that the proposed safety database for the initial BLA submission is sufficient to adequately characterize the safety of donanemab, and that it would expect the initial BLA submission to have at least 100 patients exposed to drug for ≥ 12 months, consistent with ICH E1 guidelines.

The safety database includes 6 healthy volunteers and 1402 subjects with Alzheimer's disease exposed to at least one dose of donanemab intravenously at the time of the 90-Day Safety Update. The total number exposed to monotherapy with donanemab in Study AACG is 131. If the exposure is assessed according to the protocol-based dose reductions, the exposure in Study AACG for 12 months is 97 patients with an additional 3 patients from AACH Part B. However, Dr Branagan notes that the exposure at the highest clinically relevant dose (participants who received the initial three 700 mg doses followed by the 1400 mg dose with no dose reduction) considering the all-donanemab pool and Phase 1b Study AACD was 827 at 6 months, 93 at 9 months, and 49 at 12 months, which, as Dr. Branagan notes, did not meet the advice provided to the sponsor prior to the submission of the application for "100 patients exposed to drug for ≥ 12 months, consistent with ICH E1 guidelines."

In donanemab-treated patients in Study AACG, 100% of the population were from North America. The mean and median age was approximately 75 years (range 61 to 86 years). Forty-two percent (n=55) were at least 65 to less than 75 years old, 50% were at least 75 to less than 85 years old, and 4% were at least 85 years old (although over 85 years were excluded per protocol). Fifty-one percent were women. Twenty percent (25/131) of patients were ApoE ε4 homozygotes, 53% (70/131) were heterozygotes, and 28% (36/131) were noncarriers. White patients accounted for 93% of the study population, Hispanic or Latino accounted for 4%, 1% were Asian, and Black or African American accounted for 4%. The population demographics were similar across all dose groups. Dr. Branagan notes that women, patients 85 years of age and over, as well as Hispanic or Latino, and Black patients are under-represented compared to the general Alzheimer's disease population, which may limit the interpretability of the safety outcomes with regard to these groups. Of note, demographics in the other contributory studies had some difference in demographic characteristics such as a higher percentage of Latino ethnicity in AACI.

Dr. Branagan considered the applicant's translation of adverse events from verbatim terms to preferred terms to be adequate. She notes that the protocols for the clinical studies did not have case report forms for collection of ARIA-H symptoms and that in AACG, ARIA-H was not reported as an adverse event but captured as an MRI finding; therefore, in agreement with the applicant, Dr. Branagan notes that analyses of findings from MRI, as she has reviewed, would better represent the frequency of ARIA-H than would reliance of adverse reaction datasets.

Deaths

Dr. Branagan does not identify any deaths attributable to treatment with donanemab in Studies AACG, AACH Part B, AACI Safety Addendum, or AACN-Dona Cohort. She notes that in the placebo-controlled Study AACG, there was not an excess of deaths and no clusters of unusual deaths in the donanemab arm (2/131, 0.8%, preferred terms were death and pneumonia) compared to placebo (2/125, 1.6%, aspiration pneumonia and cardiac arrest). She notes that the frequency of AEs with fatal outcome in the all-donanemab pool (4/1293, 0.3%, gunshot wound and acute respiratory failure in addition to death and pneumonia) did

not exceed that observed in the donanemab arm of AACG. She identified an additional death in the all-donanemab pool that occurred 31 days after the last dose of study drug after the cutoff date for the 90-day safety update, with cause of death pending (autopsy not performed, results for request of death certificate pending); this resulted in the incidence of deaths of 0.4% (5/1304). None of those deaths was preceded by documented ARIA.

In ongoing blinded Study AACI, Dr. Branagan reports 23 deaths, 3 of which appeared to be related to ARIA-E (Subject I5T-MC-AACI-(b) (6)), ARIA-H (Subject I5T-MC-AACI-(b) (6) (b) (6)), or reported severe ARIA-E and severe ARIA-H (Subject (b) (6)) and are described in detail in Dr. Branagan's review and briefly described below.

Subject I5T-MC-AACI-(b) (6) was a 72 year-old female, Apo E ε3/ ε4, with declining cognition for several weeks prior to the onset of ARIA-E, who was hospitalized and diagnosed with the SAE of ARIA-E with severe vasogenic edema on Day 66, 11 days after her second dose of blinded study drug. CT of the head on that day noted in the impression the following: extensive vasogenic edema throughout the right cerebral hemisphere, and probably some within the left occipital lobe remains stable with no discrete enhancing mass. An EEG on the 3rd day of hospitalization was reported as "diffusely and continually abnormal, consistent with the patient's clinical presentation of nonspecific moderately severe encephalopathy". A CT scan of the head 3 days later included an impression of "a sliver of hyperdensity within the right posterior and anterior frontal lobe sulci along the vertex suspicious for new foci of subarachnoid hemorrhage". Three days later the patient was discharged to hospice care and died on Day 79. Baseline MRI did not show any presence of ARIA-E, more than 4 cerebral microhemorrhages, macrohemorrhage, more than 1 area of superficial siderosis, or severe white matter disease. There were no post-screening MRIs. Cerebral edema was listed as cause of death. Autopsy results have not been made available.

Subject I5T-MC-AACI-(b) (6) was a 72 year-old male, Apo E ε3/ ε3 with a history that included brain trauma, migraines, hypertension, and hypercholesterolemia, who was hospitalized for unstable gait and incomprehensible speech/aphasia on Study Day 72 and diagnosed with severe cerebral hemorrhage and hemorrhage stroke with mass effect. He had taken several acetylsalicylic acid tablets (quantity and dose unknown) at the onset of aphasia. The second and last dose of blinded study medication had been 44 days before. He complained of a mild headache on Days 46 thru 45, and Day 62. MRI on Day 71 showed mild ARIA-E, ARIA H (based on presence of a new microhemorrhage), superficial siderosis in the left frontal lobe (increased from baseline of 50 mm to 65 mm), and in the right occipital, right parietal, and right temporal non-hippocampal areas (all measuring < 7 mm). A CT scan in the emergency room showed a large left parietal intraparenchymal hemorrhage and vasogenic edema, left frontotemporoparietal intraparenchymal hemorrhage of amyloid appearance with midline shift (5mm), and an adjacent subarachnoid hemorrhage. A repeat CT scan the same day showed a hematoma in the left posterior parietal region, measuring 5.5 x 4.3 cm. The patient became comatose and was transferred to palliative care and died on Day 75. The cause of death on the death certificate was hemorrhagic stroke and ARIA-H. His baseline MRI (central read) showed absence of findings contraindicating participation in the study.

Superficial siderosis was present in the left frontal region and measured 50 mm. White matter disease was present with beginning confluence of lesions. The cause of death on the death certificate was hemorrhagic stroke and ARIA-H. The Agency considers this to be categorized as an intracerebral hemorrhage.

Subject (b) (6) /Manufacturer Report # US202211015256 (initial IND safety report submitted December 23, 2022, follow-up report on December 28, 2022, and response to information request on January 5, 2023) is a 76 year-old White male from blinded main study AACI with a history including chronic kidney disease stage 3, hypertension, hyperlipidemia, type 2 diabetes mellitus, aortic arteriosclerosis, balance disorder, and heterozygous for ApoE ε4, and who had a previous episode of ARIA-E and ARIA H on Study Day 79 after 3 doses of donanemab or placebo for which dosing was temporarily stopped until Day 202, who presented to the ER (on Study Day 427) after developing increased confusion for two weeks, nausea, bowel incontinence, and vomiting. The patient was admitted for symptomatic ARIA-E and ARIA-H, and died 18 days later. Additional symptoms prior to presentation to the ER included worsening balance and headaches for two weeks. The patient had received 10 doses of study drug prior to presentation to the ER, with the most recent dose occurring 24 days before. An unscheduled MRI obtained four days before presentation to the ER (Study Day 423) showed severe ARIA-E (right frontal; left frontal; right temporal, non-hippocampal; right parietal; left parietal; right occipital) and more than 10 new microhemorrhages (43 total microhemorrhages). At baseline, the patient's MRI showed no ARIA-E, microhemorrhages, superficial siderosis, or macrohemorrhage. Vital signs upon admission to the ER included an elevated blood pressure (213/107 [units not reported]), temperature 36.9 (units not reported), pulse of 75 (units not reported), and respiratory rate of 18 (units not reported). A neurological exam showed left sided weakness and left sided neglect. The impression from a CT scan was diffuse vasogenic edema within the right cerebral hemisphere with 2 mm of right to left midline shift. An MRI the following day showed ARIA-E with extent greater than 10 cm and involvement in multiple areas of the brain (right frontal, right temporal, non-hippocampal, right parietal, right occipital, left frontal, left parietal) and greater than 10 microhemorrhages. The patient was started on dexamethasone and ondansetron and discharged to hospice that day. Ten days later, he was discharged to a skilled nursing facility where he passed 9 days later (SAE term: death of unknown cause). No autopsy was performed. He was also reported to die due to symptomatic ARIA-E and symptomatic ARIA-H. Given the conflicting information, the cause of death is to be confirmed. Receipt of the death certificate is still pending.

Additional events experienced by the patient and not included above are outlined in the table below, extracted from Dr. Branagan's review.

Table 5: Additional Events Occurring in Participant (b) (6) in Blinded Main Study AACI

Study Day	Events
79	Visit 5 (Week 12) The patient was noted to have severe ARIA-E on a scheduled MRI (right frontal; right temporal, non-hippocampal; right parietal; right occipital) and more than 10 new microhemorrhages (11 total). The study drug was temporarily discontinued on this day. The patient had had three doses of study drug with the most recent dose occurring 15 days before severe ARIA-E was diagnosed by MRI.
85	The patient developed headache (mild severity), which resolved the same day.
107	An unscheduled MRI showed that the ARIA-E had decreased in size and was still severe. Additionally, the patient had developed more than 10 new microhemorrhages (23 total microhemorrhages).
112	The patient developed balance disorder (mild severity), which resolved the same day.
135	An unscheduled MRI showed moderate ARIA-E and 1 new microhemorrhage (24 total microhemorrhages).
167	An MRI showed mild ARIA-E and no new microhemorrhages.
195	An MRI showed resolution of ARIA-E and no new microhemorrhages.
202	Study drug was resumed (Week 28, Visit 9) at a dose of 700 mg or placebo equivalent
209	The patient developed intermittent headaches and the study drug was temporarily discontinued
232	An MRI showed no ARIA and the study drug infusions were resumed at 700 mg or placebo equivalent
331	Starting with 8th infusion, the dose was adjusted to 1400 mg or placebo equivalent
427	Presentation to ER for current event

As Dr. Branagan notes, a role for donanemab cannot be established as treatment is still blinded and that whether the event of death is related to the events of ARIA is unknown, given that important information is lacking in the case, such as cause of death noted on a death certificate. The applicant is currently awaiting receipt of the death certificate.

Dr. Branagan notes that the incidence of adverse events with fatal outcome in the all-donanemab pool at the time of the 90-Day safety update was 0.4% (5/1304). She notes that the incidence of death by person-years of exposure to donanemab or donanemab/BACE-I combination at the time of the 90-day Safety Update was 7/1,000 person years (5/709 person years). That does not exceed the reported incidence from Alzheimer's disease in the US of 133.8/1,000 person years. As Dr. Branagan notes, this comparison is limited by comparing the population with early-stage Alzheimer's disease (mild cognitive impairment and mild dementia) with the overall Alzheimer's disease population inclusive of later stages.

Serious and Significant Adverse Events

In the placebo-controlled AACG, serious adverse events (SAEs) occurred with equal frequency (18%) in the donanemab (23/131) and placebo arms (22/125). The most frequently reported SAEs included pneumonia (4% for donanemab vs 1% for placebo). SAEs of ARIA-E occurred in 2 donanemab patients (2%) and none in placebo. Infusion-related reaction, pulmonary embolism, and syncope also each occurred in 2 patients on donanemab (2%) and none in placebo. In the all-donanemab pool at the time of the 90-Day Safety Update, ARIA-E (8/1304, 1%), syncope (9/1304, 1%), and pneumonia (8/1304, 1%) were the most frequently reported SAEs.

At the time of the 90-Day Safety Update, 10% (165/1727) of participants in the blinded main study of AACI reported at least 1 SAE; the most frequently reported were syncope (1%), ARIA-E (1%), and Covid-19 (1%).

Dr. Branagan describes the SAEs of ARIA-E in the Phase 2 and 3 studies AACG and AACI safety addendum, noting that 9/10 had started by Day 75, with patients having received between 1 and 5 doses of donanemab. Seven of the 10 were homozygous or heterozygous ApoE ε4 carriers. The majority were reported as recovered or resolved, with median time to recover or resolution of 67 days (10-148 days). Four cases had concurrent ARIA-H. In 4 cases, treatment included steroids. Seven of the cases resulted in hospitalization. All were symptomatic with symptoms including aphasia (n=3), headache (n=3), confusion (n=2), as well as dizziness, visual changes, and gate difficulty consistent with symptoms previously reported with other monoclonal antibodies directed against aggregated forms of beta amyloid, including aducanumab and lecanemab. She also notes 4 SAEs of ARIA-H (3 who also had SAEs of ARIA-E).

Three events of cerebral hemorrhage > 1 cm were reported in the all donanemab pool at the time of the 120-Day Safety Update (I5T-MC-AACI-(b) (6) described below, and nonserious I5T-MC-AACI-(b) (6) and I5T-MC-AACI-(b) (6) described in the ARIA section of this memo) in addition to blinded Subject I5T-MC-AACI-(b) (6) described under Deaths, above. Dr. Branagan notes an SAE of cerebral hemorrhage in 79 year-old male in ongoing study AACI (AACI-(b) (6)) with a past medical history of hypertension, coronary artery disease, bradycardia, atrial fibrillation, and hyperlipidemia, ApoE ε3ε4 genotype, and history of tobacco use, that developed on Day 74, 17 days after the 3rd dose of donanemab that was given on Day 58, and 43 days after the development of ARIA E (moderate severity with confusional state of mild severity) that started on the day of the 2nd dose of donanemab (Day 31) . Concomitant medications included apixaban, dofetilide, and lovastatin. MRI on Study Day 67 showed moderate ARIA-E in the left and right cerebellum, left and right parietal lobes, and right frontal lobe, and a lacunar infarct in the right cerebellum (5 mm). On Study Day 74, the patient lost his balance and fell on the sidewalk while running, and developed bleeding to the back of the brain, hemorrhagic stroke, worsening vision, and confusion. The patient was hospitalized on the same day for the SAE of cerebral hemorrhage (severe severity) and underwent CT without contrast and was diagnosed with a right occipital lobe

intraparenchymal hemorrhage with rupture into the right lateral ventricle and mild ventriculomegaly. The patient's partial thromboplastin time was 48.8 sec (reference range: 25.1-36.5 sec). On [redacted] (Study Day 76), the patient's prothrombin time was 13. A follow-up MRI Study Day 130 showed mild+ severity of ARIA-E with increased size in the left and right cerebellum, left and right parietal lobes, right occipital lobe, and right frontal lobe, and a macrohemorrhage of 29 mm in right occipital lobe. Partial thromboplastin time was 48.8 sec (reference range: 25.1-36.5 sec). On Study Day 76, the patient's prothrombin time was 13.3 sec (reference range: 10-12.8 sec) and international normal ratio was 1.14 (reference range: 0.8-1.1). As of the 90-Day Safety Update, the symptom of confusion associated with ARIA-E was ongoing; the SAE of cerebral hemorrhage was resolving. Dr. Branagan finds that a role for donanemab in the AE of ARIA-E is likely given temporal association with donanemab and AE onset. Contributory factors for the SAE of cerebral hemorrhage included the preceding event of fall and concomitant medication use with apixaban, although a role role for donanemab in the SAE of cerebral hemorrhage cannot be excluded given proximity of occurrence of cerebral hemorrhage with ARIA-E.

Dr. Branagan notes 1 SAE of subarachnoid hemorrhage on the same day as the 5th dose of donanemab (Day 199) in Study AACG (I5T-MC-AACG-[redacted]). The patient had an infusion-related reaction on Study Day 56 (3rd dose) and ARIA-E beginning on Study Day 78 and reported as resolved on Day 162. She had resumed treatment with donanemab on Day 171 (4th dose). On the day of the event, the patient developed an infusion reaction with flushing, feeling hot, and shortness of breath; the infusion was stopped, and the patient developed a throbbing occipital headache with blood pressure of 181/103 mm Hg. Dr. Branagan notes the infusion reaction that occurred during donanemab administration is a likely contributory factor to the SAE of subarachnoid hemorrhage.

Dr. Branagan notes 2 SAEs of seizures on treatment with donanemab or within 57 days of treatment, one of which (I5T-MC-AACI-[redacted]) occurred in the setting of metabolic encephalopathy and Covid-19 infection and which Dr. Branagan notes is unlikely to be related to donanemab. She also does not establish a role for donanemab in Subject I5T-MC-AACI-[redacted] of whom the SAE had likely contributory events of subarachnoid bleed and subdural hygroma (likely caused by preceding events of falls).

Dr. Branagan describes the 9 SAEs related to hypersensitivity and infusion-related reactions that included infusion related reaction (n=5), anaphylactic reaction (n=3, occurring within minutes after an infusion and all treated with epinephrine) and drug eruption.

Dr. Branagan describes 1 SAE of toxic encephalopathy, occurring in in 81 year-old patient on Study day 303 in which the dose of donanemab was increased to 1400 mg, with vital signs, labs, and imaging unrevealing of a specific cause of encephalopathy, and from which the patient recovered 6 days later with sequalae of increased confusion.

Dr. Branagan shows that most TEAEs in Study AACG were mild or moderate in severity based on principal investigator judgment. In the donanemab treatment group, 81% of TEAEs were

mild, 59% were moderate, and 16% were severe. Similar findings were observed for placebo. The most frequent severe TEAEs (incapacitating, with inability to work or perform normal daily activity in the donanemab group in AACG were ARIA-E that occurred in 7 patients (5%) vs 0% on placebo, infection 5 patients (4%, 3 of which were pneumonia) on donanemab vs 1 (1%) on placebo. Severe TEAEs of ARIA-H microhemorrhage and infusion related reaction each occurred in 2% on donanemab and none on placebo. At the time of the 90-Day Safety Update 6% (78/1304 participants in the all-donanemab pool had at least 1 severe TEAE. ARIA-E was the most frequently reported severe TEAE in the all-donanemab group after the 90 Day Safety update. 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.

Discontinuations Due to Adverse Events

In the placebo-controlled study AACG, 72% of patients in the donanemab group completed the study compared to 74% of patients on placebo. Adverse events leading to study withdrawal occurred in approximately 15% of patients on donanemab compared to 5% on placebo. The most frequent TEAEs leading to study withdrawal in AACG were allergic reaction/hypersensitivity and ARIA-H microhemorrhage. Treatment discontinuation occurred in approximately 37% (49/131) of patients on donanemab vs 27% (34/125) on placebo. Treatment discontinuation in the donanemab arm was driven by adverse events (31%) vs 7% in placebo. In the donanemab group these were primarily related to infusion related reactions (5%), ARIA-E (5%), ARIA-H superficial siderosis (5%), and ARIA-H microhemorrhage (4%).

At the time of the 90-Day Safety Update, adverse events leading to study withdrawal occurred in approximately 4% (56/1304) of participants in the all-donanemab pool; these were most frequently infusion related reactions (2%). TEAEs leading to treatment discontinuation were reported in 8% (100/1304) of participants in the all-donanemab pool; these were also most frequently infusion related reactions (3%).

Treatment-Emergent Adverse Events (TEAEs) of All Severities

There was no imbalance in the incidence of TEAES overall in the donanemab group (90%, 118/131) compared to placebo (90%, 112/125) in AACG. The most frequently reported TEAEs in AACG in the donanemab group were ARIA-E, ARIA-H microhemorrhage, ARIA-H superficial siderosis, and nausea/vomiting that all occurred in at least 10% and greater than placebo (see Table 6).

Table 6: TEAEs with Frequency of at least 5% and at least 2% higher in the Donanemab Arm Compared to Placebo f in Study AACG

Adverse Event	DON N=131 n (%)	Placebo N=125 n (%)
ARIA-E[1]	35 (26.7)	1 (0.8)
ARIA-H Microhemorrhage[1]	26 (19.8)	6 (4.8)
ARIA-H Superficial Siderosis[1]	22 (16.8)	3 (2.4)
Nausea/Vomiting	17 (13)	6 (4.8)
Nausea	14 (10.7)	4 (3.2)
Vomiting	7 (5.3)	3 (2.4)
Infusion Related Reaction	10 (7.6)	0
Urinary Tract Infection	13 (9.9)	5 (4)
Diarrhea	11 (8.4)	5 (4)
Anxiety	7 (5.3)	2 (1.6)

The reviewer created this using the IDB ADAE dataset submitted in a response by the applicant on August 25, 2022, to an information request dated August 2, 2022. SAFFL = Yes, StudyID=AACG, PCIN57FL = Yes, TRTEMFL= Yes.

[1]Events related to ARIA are based on ARIA events reported in the MRI dataset.

In addition to those events, Dr. Branagan notes that hypotension/orthostatic hypotension were reported more frequently in the donanemab arm compared to placebo (5% vs 2%, respectively) in the Hypotension FDA N MQG. No serious cases were identified. She notes that a higher frequency of donanemab-treated participants experienced orthostatic changes in diastolic blood pressure compared to placebo in Study AACG.

At the time of the 90-Day Safety Update, TEAEs were reported in 69% (903/1304) of participants in the all-donanemab pool. The most common TEAEs included ARIA-E (18%), ARIA-H-microhemorrhage (16%), headache (10%), infusion-related reaction (9%), and ARIA-H superficial siderosis (8%). Grouped terms related to fall, dizziness, balance disorder occurred in 9%.

Laboratory Findings

Dr. Branagan did not identify any clinically meaningful changes in laboratory values in a review of the applicant's analyses of mean change from baseline, shifts to high values, low values, and CTCAE toxicity Grades 3 through 5 for laboratory values related to chemistry or hematology. Additionally, she did not identify any clinically meaningful changes in a review of mean change from baseline and shift to abnormal for urine studies. Dr. Branagan finds that TEAEs related to laboratory findings were reported with similar frequency in donanemab and placebo arms in Study AACG. A similar frequency of participants in the donanemab and placebo arms of Study AACG had increases in AST and ALT, alkaline phosphatase, and

bilirubin in Study AACG (difference no > 1%). No donanemab-treated participants met Hy's Law.

Vital Signs

Dr. Branagan notes that higher frequencies of bradycardia, orthostatic changes in diastolic blood pressure, and TEAEs related to bradycardia and hypotension were observed in donanemab-treated participants in Study AACG. Increases and decreases in blood pressure and increases in heart rate were identified in participants experiencing infusion related reactions, as noted by Dr. Branagan in detail in the Hypersensitivity and Infusion Related Reactions section of her review. A review of mean change from baseline for vital signs, shift analyses for vital signs other than pulse rate and orthostatic diastolic blood pressure, and TEAEs related to vital signs and belonging to the SOC of Investigations did not identify a safety signal related to vital signs.

Dr. Branagan notes that a higher frequency of donanemab-treated participants had shift in heart rate from normal to less than 60 beats per minute at any visit in Study AACG (32% vs 29%, respectively). Dr. Branagan observes similar findings on ECG analyses of shift to lower heart rate. Dr. Branagan shows a higher frequency of donanemab-treated patients compared to placebo with orthostatic changes in diastolic blood pressure in AACG (overall, 18% for donanemab vs 11% for placebo. She also notes that a higher frequency of donanemab-treated participants had TEAEs of orthostatic hypotension in Study AACG (2% vs none, respectively). She notes no reports of serious cases with preferred terms of Orthostatic Hypotension in the Phase 2 and 3 Studies.

Dr. Branagan notes a trend toward a higher frequency of subjects in the donanemab arm vs placebo with weight loss of 7% or more from baseline across visits in Study AACG (14% vs 11%). She notes that the clinical significance of this finding is unknown given the small magnitude of difference in frequencies of no higher than 4% at any visit, and a similar mean decrease in weight for donanemab (0.94 kg) vs placebo (0.57 kg) by Week 76. She also notes that a review of TEAEs with the preferred term Weight Decreased showed the same frequency in the donanemab (3%, 4/131) and placebo (3%, 4/125) arms.

ECG/QT

Dr. Brangan reports a higher frequency of donanemab-treated participants was observed to have shifts in mean heart rate from normal to < 50 beats per minute (17% vs 6%, respectively); this is consistent with Vital Signs findings, above. In the all-donanemab pool this was observed in 12% of participants.

She also reports a higher frequency of donanemab-treated participants with QRS intervals to ≥ 120 msec in Study AACG. In the all-donanemab pool, a shift to QRS intervals to ≥ 120 msec was observed in 5% of participants. Dr. Branagan notes that there was no imbalance in participants reporting TEAEs related to ECG changes not related to the QT interval between donanemab and placebo arms in Study AACG.

Dr. Branagan reports that a higher frequency of donanemab-treated participants compared to placebo had mean QTcF shifts from normal to > 450 msec at any time in Study AACG (11% versus 8%, respectively). As Dr. Branagan notes, given the absence of imbalance with shifts to higher QTcF intervals, the clinical significance of the observed difference in QTcF intervals > 450 msec is unknown. In addition, Dr. Branagan notes that bradycardia and prolonged QRS intervals as reported in the present submission can confound assessment of QT interval duration and that the QT corrections may not fully correct for heart rate changes. Dr. Branagan notes that TEAEs of prolonged QT were reported in two (2%) donanemab-treated participants versus none on placebo in Study AACG. No AEs of sudden death, Torsades de Pointes, or ventricular fibrillation were reported in Phase 1 studies, Study AACG, or the all-donanemab pool.

In accordance with ICH E14 guidelines for monoclonal antibodies that have a low likelihood of direct ion channel interactions, a dedicated QT study was not conducted.

Subgroup Analyses

In general, the numbers of subjects in demographic subgroups were too low to make meaningful comparisons of differences.

Dr. Branagan finds that the incidence of ARIA-H microhemorrhage in donanemab-treated patients in AACG was higher in males compared to females (27% vs 13%, respectively). Nausea was reported with higher frequency in females (15%) compared to males (6%) as was urinary tract infection (15% vs 5%, respectively).

ARIA-E was reported with higher frequency in participants < 75 years of age (32%) vs at least 75 years of age (26%), as was nausea (15% vs 8%). ARIA-H microhemorrhage was reported with higher frequency in participants ≥ 75 years (25%) than < 75 years (18%). The number of participants less than 65 years of age was too low (10 participants) to draw conclusions regarding differences in that age group.

The number of participants with race other than White or by ethnicity other than non-Hispanic in Study AACG was too low to draw conclusions about TEAEs by race.

Dr. Branagan shows a higher frequency of ARIA-E, ARIA-H microhemorrhage, and ARIA-H superficial sideroses in donanemab-treated patients within the lowest BMI tertile compared to the highest (35% vs 20%), respectively.

Other Events of Interest

Amyloid-Relating Imaging Abnormalities (ARIA)

The following discussion refers to data from AACG unless otherwise indicated.

Table 7, extracted from Dr. Branagan's review shows the incidence of ARIA events in AACG. ARIA-E or ARIA-H may occur in isolation or concurrently. ARIA-H frequently occurs in association with an occurrence of ARIA-E.

Table 7: Number of participants with one or more Treatment Emergent ARIA Events in Study AACG)

	Donanemab N=131 N (%)	Placebo N= 125 N (%)
ARIA	49 (37)	10 (8)
ARIA-E	**35 (27)**	**1 (1)**
ARIA-H	**39 (30)**	**9 (7)**
Isolated ARIA-H[a]	14 (11)	9 (7)
Superficial Siderosis	22 (17)	3 (2)
ARIA-Microhemorrhage	26 (20)	3 (2)

[a]Isolated ARIA-H is defined as participants who had only ARIA-H and not ARIA-E during the study.

In the all-donanemab pool at the 90-Day Safety Update, the incidence of ARIA was 25% overall, the incidence of ARIA-E was 18%, the incidence of ARIA-H was 19% (superficial siderosis 85, ARIA-H microhemorrhage 16%). Dr. Branagan hypothesizes that the smaller percentage of participants with exposure of at least 6 months in the all-donanemab pool vs the AACG population may account for the observed lower incidence of ARIA in the all-donanemab pool.

In study AACG, no events of intracerebral hemorrhage greater than 1cm in diameter were reported. As noted above a fatal case of cerebral hemorrhage/hemorrhage stroke was reported in blinded Subject I5T-MC-AACI-(b) (6) Three events of intracerebral hemorrhage were reported in the all-donanemab pool (3/1304, 0.2%, all ApoE ε3ε4) in patients with risk factors but for whom a role for donanemab cannot be ruled out:

- Subject I5T-MC-AACI-(b) (6) (nonserious, 15 mm macrohemorrhage identified on a Safety MRI, 14 days after the previous dose, in the setting of ongoing asymptomatic ARIA-E in a patient with a history of hypertension, hyperlipidemia, and migraine, and taking aspirin 81 mg)
- Subject I5T-MC-AACI-(b) (6) (non-serious, 35 mm macrohemorrhage identified on a safety MRI, 174 days after the last dose, in the setting of ongoing ARIA-E, in a patient with risk factors for stroke with a history of hypertension, coronary artery disease, and hyperlipidemia, taking aspirin 81 mg and diclofenac that has a boxed warning for stroke)
- Subject AACI-(b) (6) (serious, 17 days after the 3rd dose, in the setting of ARIA-E, with history of hypertension, coronary artery disease, hyperlipidemia, concomitant medication of apixaban that has a warning for increased risk of bleeding, and with

preceding event of fall on the day of the cerebral hemorrhage, described in more detail under SAEs).

Dr. Branagan notes that symptoms of ARIA-H were not collected in the studies; therefore symptomatic ARIA is represented in Dr. Branagan's review by symptomatic ARIA-E. The majority of ARIA[2]cases in AACG were asymptomatic. Clinical symptoms were present in 5/35 (14%) of patients who had ARIA-E in the donanemab group compared to 1/1 in placebo patient who had ARIA-E. Of the 5 patients with symptoms in the donanemab arm, 1 was an ApoE ε4 homozygote, 2 were heterozygotes, and 2 were noncarriers. Symptoms in donanemab-treated participants in AACG included headache, mental status changes, cognitive disorder, nausea/vomiting, fatigue, confusion, and expressive aphasia.

In the all donanemab group as of the 90 Day Safety Update, 20% of patients with ARIA-E had clinical symptoms; the most common were headache (11%) and confusion/delirium/altered mental status/disorientation (4%). Dr. Branagan shows that most patients with ARIA-related symptoms in all-donanemab group were mild (28/229 patients, 12%) or moderate (11/229 patients, 5%) in severity, with only 1 patient with severe symptoms

Dr. Branagan notes that none of the symptoms belonged to the SMQ of convulsions among patients with ARIA but she notes that two subjects who experienced ARIA events also experienced seizures: Subject I5T-MC-AACI-(b) (6) with an SAE of seizure (treated with levetiracetam and recovered on the same day) in the setting of subarachnoid bleed and subdural hygroma 8 days after hitting her head during a fall and in the setting of moderate ARIA -H), and Subject. I5T-MC-AACI-(b) (6) who had a non-serious event of partial seizures 92 days after resolution of an ARIA-E event for which, as Dr. Branagan notes, is unlikely due to ARIA given lack of a temporal association.

Dr. Branagan did not identify any deaths in Study AACG or in the all donanemab pool in the 90-Day Safety Update due to ARIA. AS previously discussed, there were 3 deaths in the still blinded main study of AACI that were associated with ARIA (I5T-MC-AACI-(b) (6) I5T-MC-AACI-(b) (6)).

In AACG, 19% (25/131) of patients in the donanemab group were ApoE ε4 homozygotes, 53% (70/131) were heterozygotes, and 27% (36/131) were noncarriers. In AACG the incidence of ARIA-E was higher in ApoE ε4 homozygotes (11/25; 44%) than in heterozygotes (21/70; 30%) or in non-carriers (3/36; 8%) treated with donanemab (32/95; 34% in carriers overall). Similar findings were observed for ARIA-H (17/25; 68%) in homozygotes, 15/70 (21%) in heterozygotes, and 7/36 (19%) in noncarriers. Findings of increased risk of ARIA in ApoE ε4 homozygotes are consistent with observations reported for aducanumab and lecanemab. Dr. Branagan shows that radiographically severe ARIA was observed more frequently in homozygotes compared to heterozygotes or noncarriers. In the all-donanemab pool at the 90-Day Safety Update an increased risk of ARIA-E and ARIA-H in ApoE ε4 homozygotes was similarly observed.

Among the 35 patients treated with donanemab who had ARIA-E in AACG, the maximum radiographic severity was mild in 11/35 (31%), moderate in 16/35 (46%), and severe in 7/35 patients (20%). Among all 131 participants treated with donanemab in AACG the maximum radiographic severity of ARIA-E was mild in 8%, moderate in 12%, and severe in 5% of participants. Among all 131 participants treated with donanemab in AACG the maximum radiographic severity of ARIA-H microhemorrhage was mild in 15% (19/131) of patients, moderate in 2% (2/131) of patients, and severe in 4% (5/131) of patients. The maximum radiographic severity of ARIA-H superficial siderosis was mild in 9% (12/131) of patients, moderate in 2% (3/131) of patients, and severe in 5% (7/131) of patients. Among all 1304 patients treated with donanemab in the All-Donanemab Pool at the 90-Day Safety Update, the maximum radiographic severity was severe in 2% of participants for either ARIA-E, ARIA-H microhemorrhage, or ARIA-H superficial siderosis.

Routine Safety MRIs to monitor for ARIA were to be performed at screening and prior to the 2nd, 4th, 5th, 7th, 10th, and 14th infusions, as well as week 76 and early discontinuation. The MRI at Week 12/Visit 5 was to be performed and reviewed 2 weeks prior to the 4th infusion.

Table 8, extracted from Dr. Branagan's review, shows the timing of first ARIA-E events in the donanemab group in study AACG.

Table 8: Timing of first ARIA-E events in Donanemab group in study AACG

Number of Donanemab Infusions	# of Participants with First ARIA-E Event	Cumulative # Participants with 1st ARIA-E Event	Cumulative % of Participants with 1st ARIA-E Event
1	2	2	6
2	5	7	20
3	14	21	60
4	3	24	69
5	1	25	71
6	3	28	80
7	3	31	89
8	0	31	89
9	2	33	94
10	0	33	94
11	0	33	94
12	0	33	94
13	2	35	100

The majority (80%) of first ARIA-E radiographic events occurred by the 6thth dose. Similarly, in the All-Donanemab Pool at the 90-Day Safety Update, approximately 95% of ARIA-E events occurred by the 6th donanemab infusion

After detection, resolution of the first event of ARIA-E was reported in 35/35 (100%) of patients, resolving on average in 80 days (29-212 days). Resolution occurred in approximately 66% of ARIA-E patients by 12 weeks and in 89% by 21 weeks among patients who received donanemab in AACG. Resolution of symptoms was reported in 2/5 (40%) symptomatic patients in AACG. In the All -Donanamab pool at the 90-Day Safety Update, ARIA-E events resolved on average 60 days (2-212 days) after detection; resolution of the first event of ARIA was reported in 54% by 12 weeks, 69% by 20 weeks, and 71% by the end of the study. Resolution of ARIA-E symptoms in the all-donanemab pool at the time of the 90-Day Safety Update was reported in 25/45 (56%) patients.

In AACG, patients could continue on current dosing in case of mild asymptomatic ARIA-E, or continue with a dose reduction for radiographically moderate asymptomatic or radiographically mild and mild symptomatic ARIA-E. In AACG, participants who had SAEs of ARIA-E were required to permanently discontinue treatment. If ARIA-E symptoms and radiologic findings were not completely resolved within 16 weeks, the patient was permanently discontinued from donanemab treatment. Patients were also discontinued for a 2nd incidence of ARIA-E that occurred after a previous dose reduction or temporary discontinuation of donanemab. Patients were discontinued from dosing if they developed any increase in ARIA-H accompanied by clinically significant symptoms; had >4 new microhemorrhages, > 1 new area of superficial siderosis or significant worsening of pre-existing superficial siderosis; or any macrohemorrhage, regardless of symptoms. The protocols for Studies AACH Part B, AACI Safety Addendum and AACN Dona-Cohort allowed for continued dosing through ARIA during the titration period and could continue dosing for mild or moderate asymptomatic ARIA-E with monitoring. They differed from the protocol for Study AACG for indications leading to permanent discontinuation for ARIA-related conditions and included the following conditions:

- No observable resolution of moderate +/severe ARIA-E
- No observable resolution of symptomatic ARIA-E or resolution of symptoms of ARIA-E
- Symptoms of ARIA-E or ARIA-H are clearly related to a serious adverse event
- No observable resolution of symptoms of ARIA-H
- Macrohemorrhage

There is limited experience in dosing patients with multiple episodes of ARIA. Among donanemab-treated participants who experienced ARIA-E in AACG, 4/131 (3%) subjects experienced a 2nd event of ARIA-E. Among all participants in the donanemab pool who experienced ARIA-E, 18/1304 (1%) had a 2nd event and 1 patient had 3 events.

In AACG, ARIA-H in the setting of ARIA-E associated with the use of donanemab was observed in 18% (23/131) compared to no patients on placebo. Isolated ARIA-H that occurred during the study in participants who did not have ARIA E in the study occurred in 11% in donanemab-treated participants vs 7% on placebo. There were no events of cerebral hemorrhage greater than 1 cm in either donanemab or placebo treated participants in AACG. In the all donanemab pool at the time of the 90 Day Safety Update, isolated ARIA-H occurred

in 7% of patients on donanemab; 3/1304 ((< 0.5%) patients, all from the open label study AACI Safety Addendum, had cerebral hemorrhage > 1 cm.

Dr. Branagan notes that the protocol for AACG had no exclusion criteria related to antithrombotic use. Dr. Branagan shows that a similar frequency of ARIA-H microhemorrhage or superficial siderosis was observed in donanemab-treated subjects with or without concomitant antithrombotic use. She reports similar results for the all-donanemab pool. The majority of exposures to antithrombotic medications were to aspirin (82%). 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 definitive conclusions about the risk of ARIA for the use of donanemab with concurrent antithrombotic use. However, because intracerebral hemorrhages greater than 1 cm in diameter have been observed in patients taking donanemab, any future labeling should 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 donanemab.

Because risk factors for and clinical presentation of ARIA appear 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 should be considered for description in future labeling are shown in Table 9 and Table 10.

Table 9: Dosing Recommendations for Patients with ARIA-E

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

a 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.

b 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 10: Dosing Recommendations for Patients with ARIA-H

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

a 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.

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

The rationale for recommending continuation of dosing in patients with mild symptoms associated with mild radiographic ARIA-E 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 clinical judgment in determining if the presence of mild symptoms are of clinical concern and should preclude dosing with donanemab.

In patients who develop intracerebral hemorrhage greater than 1 cm in diameter during treatment with donanemab, it is recommended that dosing with donanemab be suspended until an MRI demonstrates radiographic stabilization and symptoms, if present, resolve. Prescribers should use clinical judgment in considering whether to continue treatment after radiographic stabilization and resolution of symptoms or permanently discontinue donanemab. 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.

As noted above, safety MRI monitoring in AACG was performed at screening and prior to the 2nd, 4th, 5th, 7th, 10th, and 14th infusions. The majority (80%) of first ARIA-E radiographic events occurred by the 6thth dose. Based on these observations, it is reasonable to recommend baseline (within one year) brain MRI prior to initiating treatment with donanemab with safety MRIs to check for ARIA prior to the 2nd, 3rd, 4th, and 7th infusions. Enhanced clinical vigilance for ARIA is recommended during the first 6 doses. If a patient experiences symptoms suggestive of ARIA, clinical evaluation should be performed, including MRI if indicated.

Hypersensitivity and Infusion Related Reactions
Hypersensitivity reactions (in the SMQ of Hypersensitivity, narrow) within 24 hours of an infusion were reported in 8% of patients on donanemab vs 2% on placebo in AACG, and in 9% of patients on donanemab in the all-donanemab pool. The most frequently reported TEAEs within that grouping were infusion related reactions, occurring in 10/131 (8%) of patients on donanemab vs none (0/125)_ on placebo in AACG and in 115/1304 (9%) of donanemab-treated participants in the all donanemab pool. Serious adverse reactions of infusion reactions were reported in 3/131 (2%) of patients on donanemab and none on placebo in Study AACG, and in 1% in the all-donanemab pool. Infusion related reactions led to study withdrawal in 4% and treatment discontinuation in 5% of patients on donanemab vs none on placebo, in part driven by protocol requiring permanent discontinuation in the case of prolonged acute infusion reaction. The maximum severity was mild in 60% of donanemab subjects and moderate in 47% in AACG; similarly in the all-donanemab pool, the majority were mild or moderate in severity. Hypersensitivity /infusion related reactions occurred by the 5th dose in more than 90% of participants in AACG and in all-donanemab pool. Most events occurred within 30 minutes of the end of study drug administration, although In some patients, infusion reactions and hypersensitivity reactions were reported more than 24 hours after the donanemab infusion. Anaphylaxis occurred in four patients in the all-donanemab pool (with 2 other possible cases) at the 90-Day Safety Update, including anaphylactic shock requiring treatment with epinephrine. Other infusion-related reactions included subarachnoid hemorrhage, bronchospasm, chest pain, tachycardia (including atrial fibrillation), hypotension, hypertension (including one patient with elevated blood pressure of 220/70 mm Hg followed by low blood pressure of systolic of 80 mm Hg upon standing followed by atrial fibrillation in a patient with a history of atrial fibrillation; and 1 patient with blood pressure of 240/120 mm Hg with elevated heart rate of 130 beats per minute), rash, nausea, vomiting, diarrhea, urticaria, dry cough, flushing, chills, sweating, vertigo, headache, malaise, and myalgia.

Treatment for an infusion reaction could have included slowing the infusion or treatment with epinephrine, diphenhydramine, ibuprofen, methylprednisolone, ondansetron, or acetaminophen. Following a first occurrence of an infusion reaction, 6 participants were rechallenged with donanemab, 2 of whom had premedications for at least 1 subsequent infusion, and 5 of whom had a subsequent infusion reaction on rechallenge.

Suicidal behavior/ideation
There is not a signal for suicide-related events in AACG or the all-donanemab pool. A role for donanemab in 3 suicide-related events with fatal outcomes that occurred in still blinded AACI cannot be determined.

Abuse Potential
Dr. Branagan did not identify cases of overdoses with donanemab in the all-donanemab pool. She did not identify a signal for drug abuse potential, withdrawal, or rebound.

Immunogenicity
Dr. Branagan notes that in Study AACG, 92% of donanemab patients vs 4% on placebo had treatment emergent ADA positive status. Similarly, in the all-donanemab pool, 84% (774/919) of patient evaluable for treatment emergent anti-drug antibody (ADA) responses (at least 12 weeks since first receiving donanemab) had a positive postbaseline treatment emergent ADA status. All of these participants also had neutralizing antibody present.

A higher frequency of participants with higher ADA titers compared to lower ADA titers reported a TEAE of infusion related reactions within 24 hours of a donanemab infusion (13% vs none, respectively). The low number of participants in each subgroup of ADA titer (< 50) limits the generalizability of these conclusions related to both infusion reactions and ARIA-H.

Carcinogenicity
An imbalance in the incidence of neoplasms was not identified between donanemab and placebo and Dr. Branagan did not identify a signal for human carcinogenicity or tumor development in the all-donanemab pool. However, as Dr. Branagan note, the low number of subjects with exposure to donanemab of at least 12 months or more (less than 1 year for most participants) does not allow for conclusions regarding the carcinogenic potential of donanemab in humans.

Human Reproduction and Pregnancy
There are no data on the use of donanemab in pregnant women.

Safety Summary
Although there are no observed safety issues that would preclude approval of donanemab for the proposed indication, the BLA submission contains data for only 49 patients who were exposed to donanemab at the highest proposed dosage regimen (700 mg for 3 doses followed by 1400 mg thereafter) for 12 months. The Agency had previously stated in pre-BLA meeting minutes dated November 4, 2021, that the expectation for a BLA submission is at least “100 patients exposed to drug for ≥ 12 months, consistent with ICH E1 guidelines” to adequately characterize the safety of donanemab. The applicant proposed to meet the exposure requirements through the “treatment protocol” approach based on the dosage regimen of donanemab specified in the protocol, in which the donanemab dose was either reduced or stopped when amyloid beta levels declined to a pre-specified threshold on PET imaging. Under this dosage regimen, some patients were treated with donanemab for less than 12 months but had continued safety follow-up for a year or longer; however, a substantial number of patients required a year or more of treatment with donanemab under this treatment regimen. If approved, it is anticipated that there would be a substantial number of patients with Alzheimer’s disease who will require treatment for one year or longer. Therefore, the characterization of long-term safety from 100 patients exposed to drug for at least 12 months needs to be based on patients who have had at least 12 months of continued exposure to donanemab at the highest proposed dosage regimen. Given the importance of an adequate characterization of the safety profile of donanemab when used at

its highest clinically relevant dose, the safety database is insufficient to adequately characterize the long-term safety of donanemab in the treatment of Alzheimer's disease.

ARIA is the primary observed safety issue associated with donanemab, as with lecanemab and aducanumab that are other members of this class of drugs, ARIA is characterized by radiographic findings on MRI and by symptoms associated with ARIA. Recommendations for clinical evaluation, including MRI monitoring and symptom recognition would be necessary should donanemab be approved in the future.

A future resubmission will need to consider further characterization of the risks identified in the current safety database, including:

- ARIA
- Infusion-related reactions
- Serious hypersensitivity reactions
- Immunogenicity

The applicant has not provided a summary of any educational plan for prescribers to identify patients appropriate for donanemab treatment, to identify and manage infusion related reactions, and to educate prescribers regarding ARIA or for an educational program for patients and caregivers. This should be included in any future submission.

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. Consideration should be given to referring to this registry in any future prescribing information to advise prescribers to encourage patients to enroll.

8. Advisory Committee

The application is not first-in-class, and it 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) completed inspections at 3 sites, as well as the applicant, and determined that Study AACG appears to have been conducted

adequately, and the data generated by these sites and submitted by the applicant appear acceptable in support of the respective indication.

11. Labeling

Not applicable.

12. Postmarketing Recommendations

Risk Evaluation and Management Strategies (REMS)

The Division of Risk Management is not able to make a benefit-risk determination regarding the need for a REMS because there is insufficient safety data.

Postmarketing Requirements (PMRs) and Commitments (PMCs)

Not applicable.

13. Comments to the Applicant

None.

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

/s/

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