FDA Briefing Document

BLA# 761248

Drug name: donanemab-azbt

Applicant: Eli Lilly and Company

Peripheral and Central Nervous System (PCNS) Advisory Committee Meeting

06/10/2024

Division of Neurology 1/Office of Neuroscience

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Glossary

Aβ	amyloid beta
AC	Advisory Committee
AD	Alzheimer's disease
ADAS-Cog 13	Alzheimer's Disease Assessment Scale – Cognitive Subscale
ADCS-iADL	Alzheimer's Disease Cooperative Study – instrumental Activities of Daily Living subscale
ARIA	amyloid-related imaging abnormalities
ARIA-E	ARIA with edema
ARIA-H	ARIA with hemosiderin deposition
BD	Briefing Document
BLA	biologics license application
CAA	cerebral amyloid angiopathy
CDR-SB	Clinical Dementia Rating – Sum of Boxes
CI	confidence interval
CR	complete response
FDA	Food and Drug Administration
GFAP	glial fibrillary acidic protein
iADRS	integrated Alzheimer's Disease Rating Scale
IV	intravenous
MCI	mild cognitive impairment
MMRM	mixed model with repeated measures
MMSE	Mini-mental State Examination
NCS2	Natural Cubic Spline model with two degrees of freedom
NfL	neurofilament light chain
PET	positron emission tomography
SAE	serious adverse event
SUVR	standard uptake value ratio
TEAE	treatment-emergent adverse event
vMRI	volumetric magnetic resonance imaging

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

1.1 Purpose/Objective of the AC Meeting

The FDA is convening this Advisory Committee (AC) meeting to discuss whether the data from the Phase 3 Study AACI (TRAILBLAZER-ALZ 2) support a favorable benefit-risk assessment for the use of donanemab for the treatment of Alzheimer's disease (AD).

1.2 Context for Issues To Be Discussed at the AC

AD is an irreversible and progressive neurodegenerative disease that affects memory, thinking, and behavior, and is ultimately fatal. It is the most common cause of dementia among older adults. While the causes of AD are not fully known, the disease is characterized by pathological changes in the brain, including amyloid beta plaques and neurofibrillary tangles, which precede clinical symptoms.

Approved treatments that treat the symptoms of AD include the cholinesterase inhibitors donepezil, rivastigmine, and galantamine, and the N-methyl-D-aspartate receptor antagonist, memantine. Although these treatments offer a modest benefit for the symptoms of AD, they do not target the underlying pathology of AD or change the trajectory of the disease.

Aducanumab and lecanemab are the first amyloid beta (Aβ)-directed antibodies to receive accelerated approval and traditional approval, respectively. Both aducanumab and lecanemab are indicated for the treatment of AD and the labeling states that treatment should be initiated in patients with mild cognitive impairment (MCI) or mild dementia stage of disease, the population in which treatment was studied in clinical trials. The manufacturer of aducanumab announced plans to discontinue the development and commercialization of aducanumab in 2024 for reasons unrelated to safety or efficacy. Accumulated data have demonstrated that for therapies targeting aggregated forms of Aβ there exists a relationship between reduction of brain amyloid plaque and reduction of clinical decline. Specifically, a robust reduction of brain amyloid plaque to levels consistent with a negative positron emission tomography (PET) scan has been found to be associated with a reduction in clinical decline over 18 months of approximately 20% to 40% on clinical outcome assessments of cognition and function. These data have been found by FDA to support the use of reduction of amyloid plaques on PET as a surrogate endpoint reasonably likely to predict clinical benefit in patients with early symptomatic stages of AD (e.g., mild cognitive impairment and mild dementia).

Eli Lilly and Company (Applicant) originally submitted an application for accelerated approval of donanemab based on amyloid plaque reduction in phase 2 Study AACG. That application 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 AD. The current application for traditional approval includes the results of the pivotal clinical study (Study AACI) and is intended to address the deficiencies outlined in the CR letter.

1.3 Brief Description of Issues for Discussion at the AC

On June 12, 2023, the Applicant resubmitted a biologics license application (BLA) for donanemab, a monoclonal antibody directed against brain amyloid plaque, for the treatment of AD. In support of traditional approval, the Applicant submitted results of Study AACI (TRAILBLAZER-ALZ 2). Study AACI was a double-blind, placebo-controlled study to evaluate the safety and efficacy of donanemab in

participants with early symptomatic AD. The study included a screening period of up to 7 weeks, a 76-week placebo-controlled treatment period, a 78-week extension period, and an immunogenicity and safety follow-up period of 44 weeks. A total of 1736 participants was randomized to placebo or donanemab treatment in a 1:1 ratio in the placebo-controlled period. The primary endpoint was the change from baseline in the integrated Alzheimer's Disease Rating Scale (iADRS) at 76 weeks. Secondary endpoints included the change from baseline in the Clinical Dementia Rating – Sum of Boxes (CDR-SB) and the two components of the iADRS, the Alzheimer's Disease Assessment Scale – Cognitive (ADAS-Cog 13) Subscale and the Alzheimer's Disease Cooperative Study – instrumental Activities of Daily Living (ADCS-iADL) subscale.

Study AACI employed brain tau PET imaging as an enrichment strategy to increase the proportion of participants who were likely to progress during the placebo-controlled period. Participants were required to have the presence of tau on PET imaging based on quantitative assessment and topographic deposition. Two primary analysis populations based on tau PET imaging were also specified, a low/medium tau level population and the overall population (low/medium plus high tau level population). The Applicant hypothesized that a treatment effect might be more difficult to demonstrate in participants with high tau levels due to their more advanced disease stage. The Applicant did not propose a requirement for confirmation or quantification of tau pathology in the prescribing information despite excluding participants with no or very low tau from the controlled portion of Study AACI and prioritizing a low/medium tau population in the statistical analysis.

Study AACI also allowed for cessation of donanemab dosing in the donanemab treatment arm guided by amyloid PET levels measured at 24, 52, and 76 weeks after the start of treatment. If the amyloid plaque level was <11 Centiloids on a single PET scan or 11 to <25 Centiloids on two consecutive PET scans, the participant was eligible to be switched to placebo. The Applicant theorized that cessation of donanemab dosing once brain amyloid on PET was reduced beyond a specific threshold would not adversely affect clinical outcomes. 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%, 42%, and 60%, respectively.

The primary efficacy endpoint analysis of change from baseline in iADRS at Week 76 demonstrated a statistically significant treatment effect, i.e., less decline in iADRS, in the donanemab treatment arm compared to placebo in both the low/medium tau population (3.3; 95% confidence interval [CI] 1.9, 4.6; $p<0.001$) and the overall population (2.9; 95% CI 1.5, 4.3; $p<0.001$). Statistically significant treatment effects were also demonstrated for the two components of the iADRS, ADAS-Cog 13 and ADCS-iADL. The donanemab arm also had a statistically significant reduction in decline on CDR-SB change from baseline compared to placebo in the low/medium tau population (−0.7; 95% CI −1.0, −0.4; $p<0.001$) and the overall population (−0.7; 95% CI −1.0, −0.5; $p<0.001$).

The main safety signals associated with the use of monoclonal antibodies directed against aggregated forms of beta amyloid, including donanemab, are amyloid-related imaging abnormalities (ARIA), intracerebral hemorrhage, and infusion-related reactions and hypersensitivity. Currently approved class prescribing information includes a boxed warning describing ARIA and intracerebral hemorrhage greater than 1 cm, increased risk in patients who are ApoE ε4 homozygotes, and recommendations for testing for ApoE ε4 status. The Warnings and Precautions section of the label further describes those findings, and discusses the increased risk in patients with additional risk factors for intracerebral hemorrhage including patients with findings suggestive of cerebral amyloid angiopathy (CAA) that may be present in patients with Alzheimer's disease. MRI findings consistent with CAA include more than four

microhemorrhages, intracerebral hemorrhage greater than 1 cm in diameter, more than one area of superficial siderosis, vasogenic edema, and severe white-matter disease.

ARIA is classified as ARIA with edema (ARIA-E), which can be observed on MRI as brain edema or sulcal effusions, and ARIA with hemosiderin deposition (ARIA-H), which includes microhemorrhage and superficial siderosis. Microhemorrhage and superficial siderosis, as well as mild focal edema, can occur spontaneously in patients and are commonly noted as incidental findings on MRI in individuals with Alzheimer's disease in the absence of treatment with amyloid targeting therapies; these findings may be related to underlying amyloid burden or CAA. In the setting of treatment with monoclonal antibodies directed against aggregated forms of beta amyloid, ARIA-H general occurs in association with an occurrence of ARIA-E. ARIA-H of any cause (sporadic or drug-related) and ARIA-E can occur together. ARIA is usually asymptomatic, although serious and life-threatening events, including seizure and status epilepticus, rarely can occur. When present, reported symptoms associated with ARIA may include headache, confusion, visual changes, dizziness, nausea, and gait difficulty. Focal neurologic deficits may also occur, and these can mimic stroke, necessitating an awareness by patients and physicians of the risk of ARIA in a patient exposed to this class of drugs. Symptoms associated with ARIA usually resolve over time. The presence of the ApoE ε4 allele increases the risk of ARIA, with greater risk observed in homozygotes than heterozygotes.

Consistent with the currently approved prescribing information for this class of drugs, the primary safety issues identified for donanemab in Study AACI are ARIA, cerebral hemorrhage, and infusion-related reactions and hypersensitivity, including anaphylaxis. In donanemab-treated patients in Study AACI, the incidence of ARIA-E was 24% and the incidence of ARIA-H was 31%. The risk of ARIA is increased in ApoE ε4 carriers. Two ARIA-related deaths were attributed to the use of donanemab in AACI. Intracerebral hemorrhage greater than 1 cm in diameter was reported in 0.5% of patients treated with donanemab in Study AACI. Fatal events of intracerebral hemorrhage have been observed in patients taking donanemab. The role of donanemab in a death caused by intracerebral hemorrhage cannot be ruled out although the participant had risk factors for intracerebral hemorrhage suggestive of CAA and was treated with tissue plasminogen activator in the setting of symptoms of headache and slurred speech, which may have been secondary to ARIA-E, rather than ischemic stroke. Overall, in AACI there was an imbalance in mortality that was primarily driven by ARIA-related deaths. Treatment emergent adverse events that occurred in at least 5% of participants treated with donanemab and at least 2% higher than placebo were ARIA-H microhemorrhage (25%), ARIA-E (24%), ARIA-H superficial siderosis (15%), headache (13%), and infusion related reactions (9%).

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. Because intracerebral hemorrhages greater than 1 cm in diameter have been observed in patients taking this class of medications, including donanemab, class labeling recommends additional caution when considering administration of anticoagulants or a thrombolytic agent (e.g., tissue plasminogen activator) to a patient already being treated with this class of drugs, or when considering the use of this class of drugs in patients with factors that indicate an increased risk for intracerebral hemorrhage. In addition, because ARIA-E can cause focal neurologic deficits that can mimic ischemic stroke, consideration as to whether such symptoms could be due to ARIA-E should be considered before giving thrombolytic therapy in a patient treated with donanemab.

The Agency seeks input from the AC on whether the efficacy data establish the clinical benefit of donanemab in the treatment of AD, and whether the benefit-risk assessment supports the approval of donanemab.

1.4 Draft Points for Consideration

- Consider whether the available data provide evidence of effectiveness of donanemab for the treatment of Alzheimer's disease.
  - Consider the support for effectiveness across the subgroups based on tau PET imaging.
- Consider the dosing regimen used in the clinical studies that completed treatment based on reduction of amyloid plaques on PET imaging.
  - Are there are scientific and/or clinical considerations that may factor into a decision to stop or continue dosing with donanemab if approved?
- Consider the overall benefit-risk assessment of donanemab for the treatment of Alzheimer's disease.
  - Are there subgroups of patients for whom the benefit-risk assessment may be more or less favorable?

2 Introduction and Background

2.1 Background of the Condition/Standard of Clinical Care

AD is a neurodegenerative disease that causes progressive impairments in memory, language, and thinking, with the eventual loss of ability to perform social and functional activities in daily life. Survival 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 6.9 million Americans aged 65 years and older are currently living with AD dementia, and the number is projected to grow in the absence of interventions to prevent or slow the disease (Alzheimers Association 2024).

The pathologic hallmarks of AD are extracellular deposits of Aβ, referred to as amyloid plaques, and intracellular aggregates of hyperphosphorylated tau in the form of neurofibrillary tangles. Accumulation of Aβ in the brain has been proposed to be a driver of the disease process and precedes the accumulation of tau pathology and neurodegeneration. The pathophysiological changes and clinical manifestations of AD are progressive and occur along a continuum, and accumulation of Aβ may begin 20 years or more before symptoms arise (Vermunt et al. 2019). Based on these findings, National Institute on Aging – Alzheimer's Association research criteria have been developed for the diagnosis and staging severity of AD, based on neuropathologic biomarker-based findings of the presence or absence of amyloid, tau, and evidence of neurodegeneration (Jack et al. 2018). Updates to these criteria to align clinical and research use have been proposed in response to recent developments in the field. The draft FDA guidance for industry, *Early Alzheimer's Disease: Developing Drugs for Treatment* (March 2024) also uses a biomarker-based framework along with the presence of clinical signs or symptoms (from asymptomatic to overt dementia) to define stages of AD to inform guidance for drug-development programs.

Currently approved AD treatments include the cholinesterase inhibitors donepezil, rivastigmine, and galantamine, and the N-methyl-D-aspartate antagonist memantine. Aducanumab and lecanemab received accelerated approval and traditional approval, respectively, and are indicated for the treatment of AD, specifically patients with MCI or mild dementia stage of disease.

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

2.2 Pertinent Drug Development and Regulatory History

Donanemab (previously LY3002813) is a humanized immunoglobulin G1 (IgG1) monoclonal antibody targeting the N-terminal, third amino acid, pyroglutamate formulation (N3pG) epitope that is present in brain amyloid plaques. The Applicant's proposed indication is for the treatment of AD in patients with MCI or mild dementia stage of disease. The dosing regimen is an intravenous (IV) infusion of 700 mg donanemab over approximately 30 minutes, once every 4 weeks, followed by 1400 mg every 4 weeks. The Applicant proposes cessation of dosing guided by amyloid PET levels. Donanemab is available as a 350 mg/20 mL solution in a single-dose vial for IV infusion.

Donanemab was granted Breakthrough Therapy designation for the treatment of AD in June, 2021. On May 18, 2022, the Applicant completed a BLA submission for accelerated approval based on change from baseline in brain amyloid plaque as measured by PET in phase 2 Study AACG. This application received a 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 AD. A Type A Meeting was held on March 2, 2023, and an agreement was reached on the adequacy and format of the proposed safety data to address the inadequacies noted in the CR letter. The Applicant resubmitted the BLA for traditional approval on June 12, 2023, based on results of pivotal study AACI. Study AACI was discussed at several meetings during development. Notably, the Applicant changed the primary endpoint to the iADRS during the conduct of the study and the Agency did not agree with the change (see Section 3.1.1.4).

3 Overview of Efficacy and Safety

3.1 Sources of Efficacy Data

3.1.1 Study AACI

3.1.1.1 Study Design

Study AACI was a double-blind, placebo-controlled study to evaluate the safety and efficacy of donanemab in participants with early symptomatic Alzheimer's disease. The primary objective of the study was to assess the effect of donanemab versus placebo in clinical progression as assessed by the iADRS at 76 weeks.

Study AACI comprised a screening period of up to 7 weeks, a 76-week placebo-controlled treatment period, a 78-week extension period, and an immunogenicity and safety follow-up period of 44 weeks. Participants were randomized to placebo or donanemab treatment in a 1:1 ratio in the placebo-controlled period.

Participants randomized to placebo during the double-blind period were assigned to receive donanemab in the open-label extension period and followed the same dose titration and dose cessation criteria as

participants randomized to donanemab in the double-blind period. Participants randomized to donanemab in the double-blind period continued the donanemab treatment regimen, including dose cessation, as established for the double-blind period.

A total of 277 centers across eight countries enrolled participants into Study AACI.

3.1.1.2 Population

The protocol did not specify a formal clinical diagnosis of Alzheimer's disease, but the inclusion criteria were consistent with a diagnosis of mild cognitive impairment (MCI) due to Alzheimer's disease or mild Alzheimer's disease dementia based on operationalized criteria from the 2018 National Institute on Aging at the National Institutes of Health and the Alzheimer's Association Research Framework for Alzheimer's disease (Jack et al. 2018). Participants were required to have evidence of Aβ pathology by quantitative assessment on PET (≥37 Centiloids) and evidence of tau pathology (topographic disposition consistent with moderate AD and standard uptake value ratio (SUVR) ≥1.10 or topographic disposition consistent with advanced AD). Participants were also required to have gradual and progressive change in memory function for at least 6 months and an Mini-mental State Examination (MMSE) score of 20 to ≤28.

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 SUVR according to the following:

- Low/medium tau: SUVR ≤1.46 and a topographic deposition pattern consistent with advanced AD or 1.10 ≤SUVR ≤1.46 and a topographic deposition consistent with moderate AD.
- High tau: SUVR >1.46 and a topographic deposition pattern consistent with either moderate or advanced AD.

Participants with no or very low tau were excluded from the placebo-controlled portion of Study AACI, but were eligible to enroll in the Study AACI Safety Addendum (see Section 3.1.1.2.1, below).

3.1.1.2.1 Study AACI Safety Addendum

A safety addendum was added to Study AACI to collect open-label safety data in up to approximately 1000 participants with early symptomatic Alzheimer's disease who had evidence of amyloid pathology. Participants 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. Participants 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 noneligible tau PET scan or noneligible amyloid PET scan if the amyloid level was between 24.3 and 37.1 Centiloids. Clinical efficacy assessments (e.g., CDR-SB) were not collected in the safety addendum; however, change in brain amyloid plaque deposition and blood-based biomarkers were included as endpoints.

3.1.1.3 Dosing Regimen

IV infusions of donanemab or placebo were administered over a minimum of 30 minutes every 4 weeks for up to 72 weeks. Participants were to receive 700 mg every 4 weeks for the first three doses, then 1400 mg every 4 weeks up to Week 72. The original protocol did not include a titration period. Based on two cases of symptomatic ARIA observed early in the study, the protocol was amended to incorporate a titration schedule of 700 mg for the first three doses. A total of 43 participants received 1400 mg as their initial dose before the protocol was amended.

Double-blind dose cessation of donanemab was guided by amyloid PET levels measured at Week 24, Week 52, and Week 76. Participants treated with donanemab could switch to placebo if their amyloid level was <11 Centiloids on PET at any single visit, or ≥11 to <25 Centiloids on PET at two consecutive visits.

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 participants 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.

3.1.1.4 Endpoints

The following endpoints were prespecified.

Primary Efficacy Endpoint

The primary endpoint was the change from baseline in iADRS at Week 76. The iADRS is a linear combination of 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).

The study was initially designed with the CDR-SB as the primary endpoint, but was changed during the conduct of the study. 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." In a postmeeting note, the Division also stated, "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." The Division reiterated its concerns with the use of iADRS as the primary endpoint at the December 22, 2022, Type B Meeting.

Select Secondary Clinical Efficacy Endpoints

Clinical Dementia Rating – Sum of Boxes (CDR-SB) Change From Baseline at Week 76

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

ADAS-Cog 13 Change From Baseline at Week 76

The ADAS-Cog 13 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.

ADCS-iADL Change From Baseline at Week 76

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 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.

Pharmacodynamic Markers

Key biomarker and pharmacodynamic endpoints included the following:

- 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 six 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 (multiblock 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).

3.1.1.5 Statistical Analyses

The analyses described below were prespecified.

Clinical Endpoints

A Natural Cubic Spline model with two degrees of freedom (NCS2) was used to assess the difference between treatment groups for the endpoints of iADRS, ADAS-Cog 13, and ADCS-iADL change in baseline at Week 76. For the NCS2 model, two knots were placed at the minimum and maximum observations times and one knot was placed at the median observation time. The baseline estimates 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 postbaseline visits. The model included fixed effect terms for NCS expansion terms (two terms), NCS basis expansion term-by-treatment interaction (two terms), baseline age, use of AD medication at baseline (yes or no), and pooled investigator. Baseline tau category (low/medium or high) was included as a covariate in the model applied to the overall population. An unstructured variance-covariance structure matrix was assumed for the within-participant variance-covariance errors.

A mixed model with repeated measures (MMRM) was used to assess the difference between treatment groups in CDR-SB change in baseline at Week 76. The model included fixed effect 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. An unstructured variance-covariance structure matrix was assumed for the within-participant variance-covariance errors.

NCS2 and MMRM assumed measurements after death and missing data were missing at random.

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

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 tau plus high tau (defined by visual assessment and SUVR >1.46). For efficacy analyses, the primary analysis set was the Evaluable Efficacy analysis set, defined as all randomized participants with a baseline and at least one postbaseline efficacy scale. Participants were summarized according to the treatment group to which they were randomized.

The occurrence of ARIA-E and infusion-related reaction might potentially lead to functional unblinding of the study treatment. In a sensitivity analysis, iADRS measurements were censored after the first occurrence of ARIA-E or infusion-related reaction. NCS2 was fitted to this censored dataset.

Biomarker Endpoints

Change from baseline in brain amyloid deposition through Week 76 was evaluated using an MMRM model. The model included the fixed effects terms: treatment, visit, treatment-by-visit interaction, baseline Centiloid, baseline Centiloid-by-visit interaction, and age at baseline. Change from baseline in tau PET at Week 76 was assessed by an ANCOVA analysis with the model adjusted by treatment, baseline tau PET SUVR, and age at baseline. Change in vMRI at Week 76 was assessed with an MMRM model adjusting for fixed effects of treatment, baseline vMRI, and age at baseline. Change in fluid biomarkers (p-tau 217, p-tau 181, GFAP, and NfL) at Week 76 was assessed with an MMRM model adjusting for fixed effects of treatment, visit, and treatment-by-visit interactions, baseline value, baseline value-by-visit interaction and age at baseline. Baseline tau category was included as a fixed effect in all models applied to the overall population. Biomarker values may be log transformed.

3.1.2 Study AACG

3.1.2.1 Study Design

Study AACG was a phase 2 multicenter, randomized, double-blind, placebo-controlled, parallel group study in participants with early symptomatic AD. 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. Participants were initially randomized to donanemab monotherapy, donanemab in combination with LY3202626 (a BACE1 inhibitor), or placebo in a 1:1:1 ratio. Early in the study, the combination therapy arm was discontinued with only 15 participants randomized to this group.

3.1.2.2 Population

The population enrolled in the study was consistent with the low/medium tau population enrolled in Study AACI.

3.1.2.3 Dosing Regimen

Participants were to receive 700 mg every 4 weeks for the first three doses, then 1400 mg every 4 weeks up to Week 72. Double-blind 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 two consecutive scans, donanemab was switched to placebo for all subsequent administrations.

3.1.2.4 Endpoints

The primary endpoint was the change from baseline in iADRS at Week 76. Prespecified secondary endpoints were CDR-SB, ADAS-Cog 13, ADCS-iADL, and MMSE. Change from baseline in amyloid brain deposition through 76 weeks as measured by PET was included as a biomarker endpoint.

3.2 Efficacy Results

3.2.1 Efficacy Results for AACI

3.2.1.1 Disposition, Demographics, and Baseline Characteristics

A total of 8240 participants was screened for entry into the study and 1736 were randomized (876 placebo, 860 donanemab). The most common reasons for screen failure reported by the Applicant were failure to meet the inclusion criteria for amyloid PET (25%), tau PET (25%), and MMSE (23%). Of the 1736 participants randomized, 173 participants (20%) receiving placebo and 231 participants (27%) receiving donanemab discontinued from the study. The rates of discontinuation by reason between the arms were similar except for withdrawal by participant (11% placebo, 13% donanemab) and adverse event including death (4% placebo, 8% donanemab). There were 12 participants (5 placebo, 7 donanemab) who did not complete a final visit prior to the data lock. The Kaplan–Meier plot of time to study discontinuation showed that participants treated with donanemab were more likely to discontinue compared to placebo (Figure 7).

Of the randomized participants, 99% received at least one dose of treatment (874 placebo, 853 donanemab), and 74% participants completed treatment (79% placebo, 69% donanemab). Kaplan-Meier plot of time to treatment discontinuation showed that participants treated with donanemab were more likely to discontinue compared to placebo (Figure 8). Not counting 19 participants who were randomized but did not get treatment or who were still on treatment by the data cutoff date, 7% of participants who discontinued treatment were followed up and completed the study.

A total of 137 participants (52 placebo, 85 donanemab) were not included in the evaluable efficacy analysis set (ESS) for the primary endpoint of iADRS, because they did not have a baseline assessment and at least one postbaseline iADRS assessment. There were 50 participants (20 placebo, 30 donanemab) missing a baseline iADRS assessment.

At baseline, the overall population (all randomized participants) was 57% female, had a mean age of 73 years, was predominately white (92%), and African American and Hispanic patients were underrepresented. Overall, 72% of participants were enrolled in the United States. Most participants (61%) were receiving concomitant medications for AD, and 70% were ApoE4 carriers. The low/medium tau population comprised 68% of the randomized participants. Baseline demographics and disease characteristics were reasonably balanced between the treatment groups and reflected a population early in the course of AD.

Table 1. Baseline Demographics and Disease Characteristics, Randomized Population, Study AACI

	Low/Medium Tau Population			Overall Population		
	Placebo N=594	Donanemab N=588	Total N=1182	Placebo N=876	Donanemab N=860	Total N=1736
Demographic/Characteristic	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**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%)

	Low/Medium Tau Population			Overall Population		
	Placebo	Donanemab	Total	Placebo	Donanemab	Total
	N=594	N=588	N=1182	N=876	N=860	N=1736
Demographic/Characteristic	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Laboratory ApoE ε4 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%)
Noncarrier	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 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 (minimum, maximum)	23.0 (6.0, 30.0)	23.0 (12.0, 30.0)	23.0 (6.0, 30.0)	22.0 (6.0, 30.0)	23.0 (11.0, 30.0)	22.0 (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%)
Baseline tau PET (SUVR)						
Mean (SD)	1.2 (0.1)	1.2 (0.1)	1.2 (0.1)	1.3 (0.3)	1.3 (0.2)	1.3 (0.3)
Median (minimum, maximum)	1.2 (0.8, 1.5)	1.2 (0.9, 1.5)	1.2 (0.8, 1.5)	1.3 (0.8, 2.5)	1.3 (0.9, 2.2)	1.3 (0.8, 2.5)
Missing	0	0	0	58 (6.6%)	44 (5.1%)	102 (5.9%)

Source: adsl.xpt (created by the Reviewer).

Abbreviations: AD, Alzheimer's disease; ApoE, apolipoprotein E; CDR, Clinical Dementia Rating; MMSE, Mini-mental State Examination; PET, positron emission tomography; SD, standard deviation; SUVR, standard uptake value ratio

3.2.1.2 Primary Efficacy Endpoint

The primary efficacy endpoint analysis of change from baseline in iADRS at Week 76 demonstrated a statistically significant treatment effect, i.e., less decline in iADRS, in the donanemab treatment arm compared to placebo in both the low/medium tau population (3.3; 95% CI 1.9, 4.6; p<0.001) and the overall population (2.9; 95% CI 1.5, 4.3; p<0.001) (Table 2, Figure 1). Note that subjects with a high tau level was a pre-specified subgroup that was not powered to detect a treatment effect. The estimate for change from baseline in iADRS at Week 76 comparing donanemab to placebo in the high tau level subgroup (1.3; 95% CI -1.8, 4.3) numerically favored donanemab treatment, but has less precision (wider confidence interval) compared to the overall population (see Section 3.2.1.5 Subgroup Analyses).

Table 2. Primary Endpoint Analysis of iADRS Change From Baseline at Week 76, Study AACI

	Low/Medium Tau Population		Overall Population	
Variable	**Placebo (N=594)**	**Donanemab (N=588)**	**Placebo (N=876)**	**Donanemab (N=860)**
Baseline, n (%)[1]	560 (94%)	533 (91%)	824 (94%)	775 (90%)
Baseline, mean (SD)	106.0 (13.4)	105.9 (13.7)	103.8 (13.9)	104.6 (13.9)
Week 76, n (%)[2]	444 (75%)	418 (71%)	653 (75%)	583 (68%)
Week 76, mean (SD)	98.9 (18.0)	101.3 (18.2)	93.8 (20.4)	97.0 (20.9)
Change from baseline, adjusted mean[3] (SE)	−9.3 (0.5)	−6.0 (0.5)	−13.1 (0.5)	−10.2 (0.5)
Percentage slowing[4]		−35%		−22%
Difference, adjusted mean[3] (95% CI)		3.3 (1.9,4.6)		2.9 (1.5, 4.3)
p-Value		p<0.001		p<0.001

Source: Clinical Study Report Table AACI.5.2, Table AACI.5.3; findings reproduced by the Statistical Analyst

[1] Number of randomized participants with a baseline and at least one postbaseline efficacy score

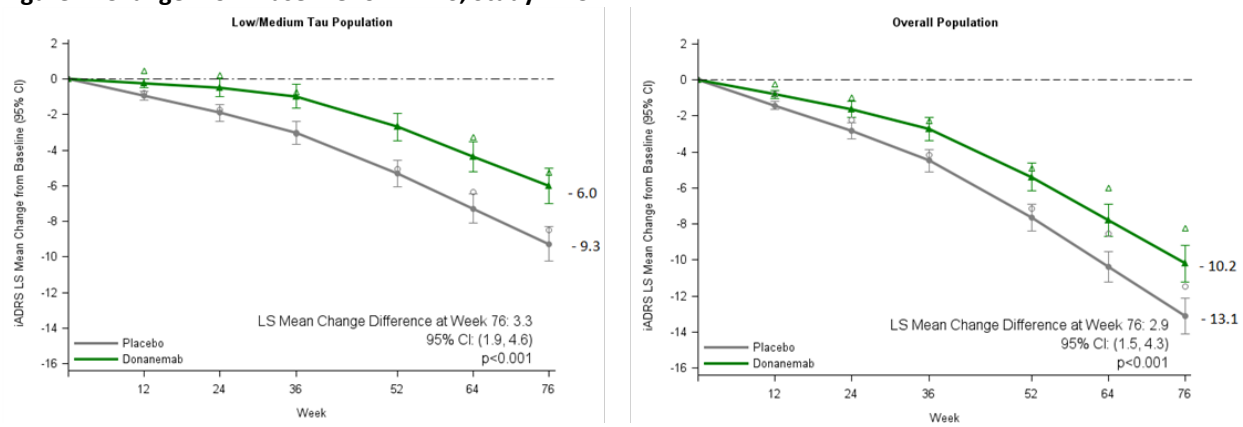
[2] Number of randomized participants with a baseline and a Week 76 efficacy score

Adjusted mean is from natural cubic spline model (NCS2) that adjusted for NCS basis expansion terms, NCS basis expansion term-by-treatment interaction, baseline age, baseline concomitant AchEI or memantine use, and pooled investigator. For the analysis of overall population, baseline tau category was also included as a covariate.

Percentage slowing: the difference of NCS2 estimates of mean change from baseline between treatment groups at Week 76 divided by the NCS2 estimate of mean change from baseline value of the placebo group.

Abbreviations: AchEI, acetylcholinesterase inhibitor; CI, confidence interval; iADRS, integrated Alzheimer's Disease Rating Scale; N, number of randomized participants; n, number of participants with a given variable; SD, standard deviation; SE, standard error

Figure 1. Change From Baseline for iADRS, Study AACI



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

3.2.1.3 Secondary Clinical Endpoints

ADAS-Cog 13 and ADCS-iADL

The donanemab arm had a statistically significant reduction in decline on ADAS-Cog 13 change from baseline at Week 76 compared to placebo in the low/medium tau population (−1.5; 95% CI −2.3, −0.8; p<0.001) and the overall population (−1.3; 95% CI −2.1, −0.6; p<0.001) (Table 3).

Table 3. Analysis of ADAS-Cog 13 Change From Baseline at Week 76, Study AACI

	Low/Medium Tau Population		Overall Population	
Variable	**Placebo (N=594)**	**Donanemab (N=588)**	**Placebo (N=876)**	**Donanemab (N=860)**
Baseline, n (%)[1]	570 (96%)	550 (94%)	841 (96%)	797 (93%)
Baseline, mean (SD)	27.6 (8.2)	27.4 (8.4)	29.2 (8.9)	28.5 (8.8)
Week 76, n (%)[2]	460 (77%)	431 (73%)	677 (77%)	607 (71%)
Week 76, mean (SD)	31.2 (10.4)	29.8 (10.7)	34.5 (12.0)	32.7 (12.4)
Change from baseline, adjusted mean[3] (SE)	4.7 (0.3)	3.2 (0.3)	6.8 (0.3)	5.5 (0.3)
Percentage slowing[4]		−32%		−20%
Difference, adjusted mean[3] (95% CI)		−1.5 (−2.3, −0.8)		−1.3 (−2.1, −0.6)
p-Value		p<0.001		p<0.001

Source: Clinical Study Report Tables AACI.5.8 and AACI.5.9; findings reproduced by the Statistical Analyst.

[1] Number of randomized participants with a baseline and at least one postbaseline efficacy score.

[2] Number of randomized participants with a baseline and a Week 76 efficacy score.

[3] Adjusted mean is from natural cubic spline model (NCS2) that adjusted for NCS basis expansion terms, NCS basis expansion term-by-treatment interaction, baseline age, baseline concomitant AchEI or memantine use, and pooled investigator. For the analysis of overall population, baseline tau category was also included as a covariate.

[4] Percentage slowing: the difference of NCS2 estimates of mean change from baseline between treatment groups at Week 76 divided by the NCS2 estimate of mean change from baseline value of the placebo group.

Abbreviations: AchEI, acetylcholinesterase inhibitor ADAS-Cog 13, 13-item Alzheimer's Disease Assessment Scale—Cognitive Subscale; CI, confidence interval; N, number of participants; n, number of participants with a given variable; SD, standard deviation; SE, standard error

The donanemab arm had a statistically significant reduction in decline on ADCS-iADL change from baseline at Week 76 compared to placebo in the low/medium tau population (1.8; 95% CI 0.9, 2.7; p<0.001) and the overall population (1.7; 95% CI 0.8, 2.6; p<0.001) (Table 4).

Table 4. Analysis of ADCS-iADL Change From Baseline at Week 76, Study AACI

	Low/Medium Tau Population		Overall Population	
Variable	Placebo (N=594)	Donanemab (N=588)	Placebo (N=876)	Donanemab (N=860)
Baseline, n (%)[1]	562 (95%)	535 (91%)	826 (94%)	780 (91%)
Baseline, mean (SD)	48.6 (7.7)	48.2 (7.9)	48.0 (7.7)	48.0 (7.9)
Week 76, n (%)[2]	451 (76%)	420 (71%)	661 (75%)	591 (69%)
Week 76, mean (SD)	45.1 (9.8)	46.1 (10.3)	43.3 (10.6)	44.5 (11.1)
Change from baseline, adjusted mean[3] (SE)	−4.6 (0.3)	−2.8 (0.3)	−6.1 (0.3)	−4.4 (0.3)
Percentage slowing[4]		−40%		−28%
Difference, adjusted mean[3] (95% CI)		1.8 (0.9, 2.7)		1.7 (0.8, 2.6)
p-Value		p<0.001		p<0.001

Source: Clinical Study Report Tables AACI.5.10 and AACI.5.11; findings reproduced by the Statistical Analyst.

[1] Number of randomized participants with a baseline and at least one postbaseline efficacy score.

[2]Number of randomized participants with a baseline and a Week 76 efficacy score.

[3] Adjusted mean is from natural cubic spline model (NCS2) that adjusted for NCS basis expansion terms, NCS basis expansion term-by-treatment interaction, baseline age, baseline concomitant AchEI or memantine use, and pooled investigator. For the analysis of overall population, baseline tau category was also included as a covariate.

[4] Percentage slowing: the difference of NCS2 estimates of mean change from baseline between treatment groups at Week 76 divided by the NCS2 estimate of mean change from baseline value of the placebo group.

Abbreviations: AchEI, acetylcholinesterase inhibitor ADCS-iADL, Alzheimer's Disease Cooperative Study—instrumental Activities of Daily Living subscale; CI, confidence interval; N, number of participants; n, number of participants with a given variable

CDR-SB

The donanemab arm had a statistically significant reduction in decline on CDR-SB change from baseline at Week 76 compared to placebo in the low/medium tau population (−0.7; 95% CI −1.0, −0.4; p<0.001) and the overall population (−0.7; 95% CI −1.0, −0.5; p<0.001) (Table 5, Figure 2).

Table 5. Analysis of CDR-SB Change From Baseline at Week 76, Study AACI

	Low/Medium Tau Population		Overall Population	
Variable	Placebo (N=594)	Donanemab (N=588)	Placebo (N=876)	Donanemab (N=860)
Baseline, n (%)[1]	569 (96%)	546 (93%)	838 (96%)	794 (92%)
Baseline, mean (SD)	3.6 (2.0)	3.7 (2.1)	3.9 (2.0)	3.9 (2.1)
Week 76, n (%)[2]	459 (77%)	424 (72%)	672 (77%)	598 (70%)
Week 76, mean (SD)	5.1 (2.9)	4.6 (2.9)	5.8 (3.2)	5.3 (3.2)
Change from baseline, adjusted mean[3] (SE)	1.9 (0.1)	1.2 (0.1)	2.4 (0.1)	1.7 (0.1)
Percentage slowing[4]		−36%		−29%
Difference, adjusted mean[3] (95% CI)		−0.7 (−1.0, −0.4)		−0.7 (−1.0, −0.5)
p-Value		p<0.001		p<0.001

Source: Clinical Study Report Tables AACI.5.6 to AACI.5.11; findings reproduced by the Statistical Analyst.

[1] Number of randomized participants with a baseline and at least one postbaseline efficacy score.

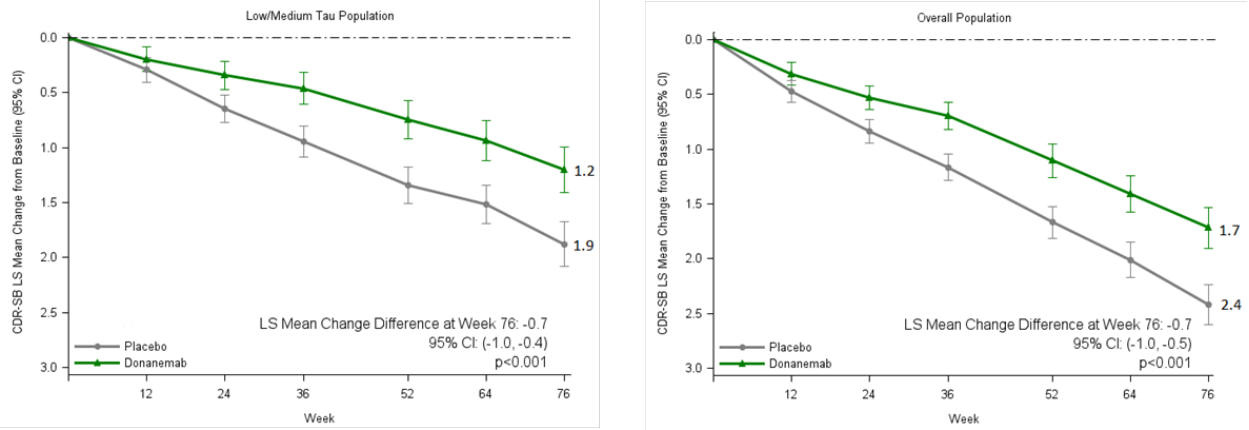
[2] Number of randomized participants with a baseline and a Week 76 efficacy score.

Adjusted mean is from the mixed model with repeated measures (MMRM) that adjusted for treatment, visit, treatment-by-visit interaction, baseline CDR-SB score, baseline score-by-visit interaction, age at baseline, and concomitant AChEI and/or memantine use at baseline, and pooled investigator. For the analysis of overall population, baseline tau category was also included as a covariate.

Percentage slowing: The difference of MMRM estimates of mean change from baseline between treatment groups at Week 76 divided by the MMRM estimate of mean change from baseline value of the placebo group.

Abbreviations: AchEI, acetylcholinesterase inhibitor; CDR-SB, Clinical Dementia Rating-Sum of Boxes; CI, confidence interval; N, number of randomized participants; n, number of participants with a given variable; SD, standard deviation; SE, standard error

Figure 2. Change From Baseline for CDR-SB, Study AACI



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

To address the potential effect of functional unblinding due to ARIA or infusion reactions, the primary analysis (NCS2) was conducted on a reduced dataset in which all assessments after occurrence of ARIA-E or infusion reaction were excluded. A definitive conclusion cannot be reached by such an analysis due to the lack of a balanced control group, including balance with respect to follow-up time, but the results (iADRS mean change difference 2.1; 95% CI 0.5, 3.7; overall population) were consistent with the primary analysis and did not appear to suggest a systematic bias due to functional unblinding. It is also worth noting that steps were taken in the protocol to minimize functional unblinding, specifically the use of an independent rater who was blinded to the patient's evaluations, including imaging results. Also, ARIA and infusion reactions occurred in both donanemab and placebo arms, suggesting that investigators could not, with complete accuracy, know the patient's treatment group based on occurrence of an ARIA event.

3.2.1.4 Biomarker Endpoints

Amyloid PET

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; 95% CI −91.2, −85.2; p<0.0001) and the overall population (−86.4; 95% CI −88.9, −83.9; p<0.0001) (Table 6). The results indicate a time-dependent relationship (Figure 3).

Table 6. Pharmacodynamic Endpoint Analysis (Amyloid PET), Overall Population, Study AACI

Variable	Placebo (N=876)	Donanemab (N=860)
Baseline, n (%)[1]	812 (93%)	765 (89%)
Baseline, mean (SD)	101.8 (34.4)	104.0 (34.4)
Week 76, n (%)[2]	690 (79%)	614 (71%)
Week 76, mean (SD)	101.8 (35.7)	15.0 (22.8)
Change from baseline, adjusted mean[3] (SE)	−0.7 (0.9)	−87.0 (1.0)
Difference, adjusted mean[3] (95% CI)		−86.4 (−88.9, −83.9)
p-Value		p<0.0001

Source: Clinical Study Report Table AACI.8.45; findings reproduced by the Statistical Analyst.

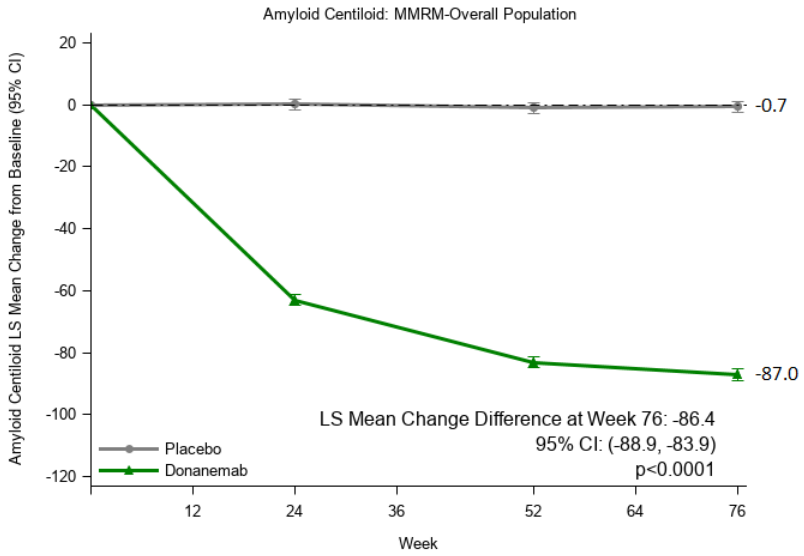
[1] Number of randomized participants with a baseline and at least one postbaseline efficacy score

[2] Number of randomized participants with a baseline and a Week 76 efficacy score.

[3] Adjusted mean is from the mixed model with repeated measures that adjusted for treatment, visit, treatment-by-visit interaction, baseline Centiloid, baseline Centiloid-by-visit interaction, and baseline age, and baseline tau category.

Abbreviations: CI, confidence interval; N, number of randomized participants; n, number of participants with a given variable; PET, positron emission tomography; SD, standard deviation; SE, standard error

Figure 3. Change From Baseline in Brain Amyloid (Centiloids), Overall Population, Study AACI



Source: Statistical Analyst.

Abbreviations: CI, confidence interval; LS, least squares

Tau PET

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 (0.0002; 95% CI −0.010, 0.010; p=0.97) or the overall population (−0.004; 95% CI −0.015, 0.007; p=0.45) (Table 7). 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.

Table 7. Summary of Tau PET Analysis, Week 76, Study AACI

Region	Baseline SUVR		LS Mean Change From Baseline (Week 76)		Difference From Placebo (95% CI)
	Donanemab	Placebo	Donanemab	Placebo	
Low/medium tau population	N=404	N=452	N=404	N=452	
Frontal	1.1709	1.1696	0.0273	0.0271	0.0002 (−0.0100, 0.0104)
Posterior lateral temporal	1.4923	1.4867	0.0634	0.0698	−0.0064 (−0.0207, 0.0078)
Parietal	1.2594	1.2667	0.0521	0.0555	−0.0034 (−0.0160, 0.0091)
AD Signature-weighted	1.4850	1.4811	0.0692	0.0706	−0.0015 (−0.0154, 0.0124)
Overall population	N=578	N=654	N=578	N=654	
Frontal	1.2775	1.2738	0.0401	0.0442	−0.0041 (−0.0148, 0.0066)
Posterior lateral temporal	1.6645	1.6266	0.0503	0.0617	−0.0114 (−0.0257, 0.0029)
Parietal	1.4272	1.4146	0.0478	0.0553	−0.0074 (−0.0206, 0.0058)
AD Signature-weighted	1.6573	1.6334	0.0636	0.0701	−0.0065 (−0.0208, 0.0078)

Source: Tables AACI.8.52, AACI.8.53, AACI.8.54, and AACI.8.55 from the Study AACI Clinical Study Report and APP.1.1, APP.1.2, APP.1.3, and APP.1.4 in a September 29, 2023, response to an Information Request.

Abbreviations: AD, Alzheimer's disease; CI, confidence interval; LS, least squares; N, number of participants; PET, positron emission tomography; SUVR, standard uptake value ratio

vMRI

Donanemab treatment was associated with a decrease in whole brain volume and an increase in ventricular volume at Week 76 (Table 8). Similar changes have been observed with other monoclonal antibodies that target amyloid. Although decreases in brain volume can reflect atrophy or neurodegeneration, the physiologic or pathologic changes that underly the observed changes in brain volume with monoclonal antibodies targeting amyloid are unclear. Change in brain volume is a nonspecific finding that could reflect a number of different underlying physiologic processes related to amyloid removal. It is also notable that, in contrast to the whole brain and ventricular volume changes, donanemab treatment appears to be associated with a reduction in loss of total hippocampal volume. The clinical relevance of the observed changes in whole brain and ventricular volumes are unclear, particularly in light of the favorable results on clinical endpoints observed in Study AACI. It will be important to collect longer-term data in a large number of patients to further understand the clinical implications, if any, of these observations.

Table 8. Summary of vMRI Analysis, Week 76, Study AACI

Region	Baseline (cm^3)		LS Mean Change From Baseline (Week 76)		Difference From Placebo (95% CI)
	Donanemab	Placebo	Donanemab	Placebo	
Low/medium tau population	n=535	n=565	n=381	n=414	
Hippocampus	6.23	6.19	−0.21	−0.22	0.02 (0, 0.03)
Whole brain	970	981	−24	−18	−6 (−8, −5)
Ventricles	48.24	50.22	8.46	6.07	2.40 (1.88, 2.91)
Overall population	n=786	n=831	n=547	n=606	
Hippocampus	6.23	6.20	−0.20	−0.22	0.02 (0.01, 0.04)
Whole brain	971	975	−27	−21	−7 (−8, −6)
Ventricles	49.39	50.39	10.07	7.05	3.02 (2.52, 3.52)

Source: Tables AACI.8.56 and AACI.8.57 from the Study AACI Clinical Study Report.

Abbreviations: CI, confidence interval; LS, least squares, vMRI, volumetric magnetic resonance imaging

Fluid Biomarkers

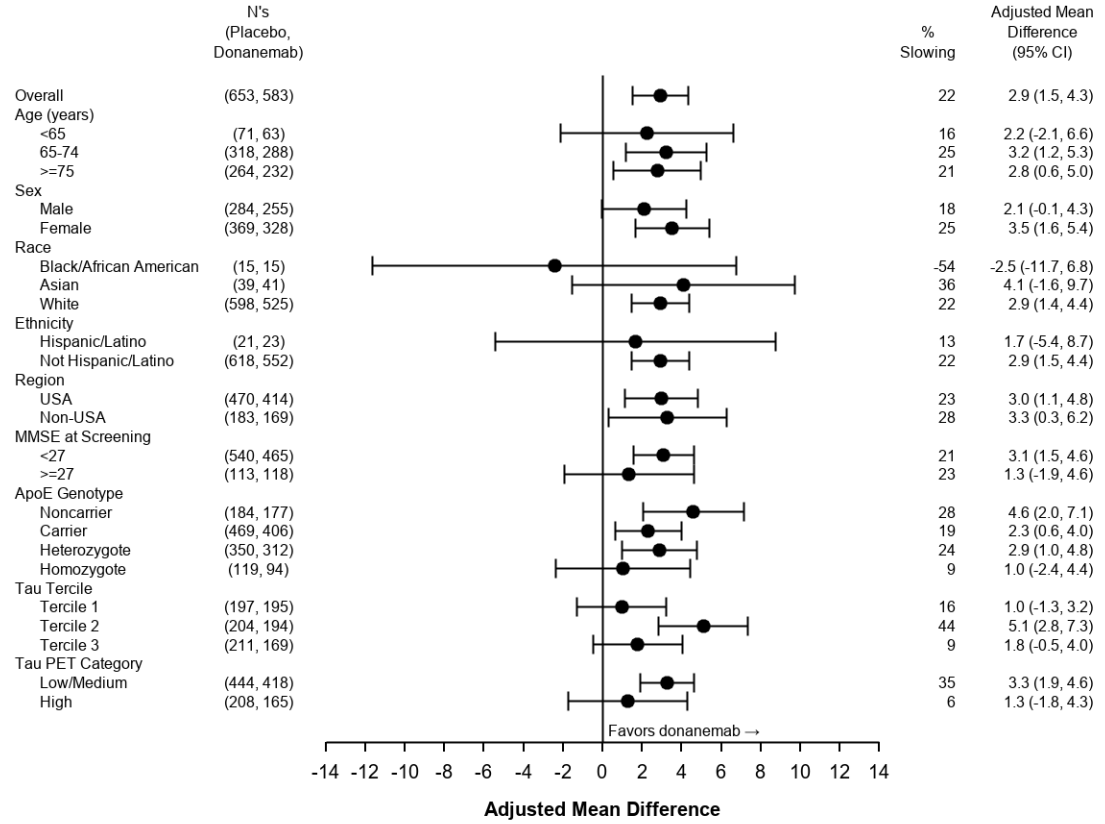
Donanemab treatment was associated with a decrease in p-tau 217, p-tau 181, and GFAP compared to placebo at Week 76. No treatment difference was observed for plasma NfL at Week 76, but a larger increase was observed in the donanemab arm compared to placebo at Weeks 12 and 24.

3.2.1.5 Subgroup Analyses

Prespecified subgroup analyses were performed across demographic and baseline disease characteristics (Figure 4 and Figure 5) for change in baseline in iADRS and CDR-SB at Week 76. 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 estimates and favor treatment with donanemab.

Of note are the subgroup estimates of the subjects with a high tau level. Consistent with the overall population estimate but with lower precision, subjects with a high tau level had an estimate favoring treatment with donanemab on iADRS (1.3; 95% CI -1.8, 4.3) and CDR-SB (-0.7, 95% CI -1.2, -0.2).

Figure 4. Subgroup Analyses for iADRS Change From Baseline at Week 76, Study AACI



Source: Statistical Analyst.

ApoE genotype (number of E4 alleles): Noncarrier (0), heterozygote (1), homozygote (2).

Tau tertile: Tertile 1 (SUVR <33 percentile), tertile 2 (SUVR 33-67 percentile), tertile 3 (SUVR >67 percentile).

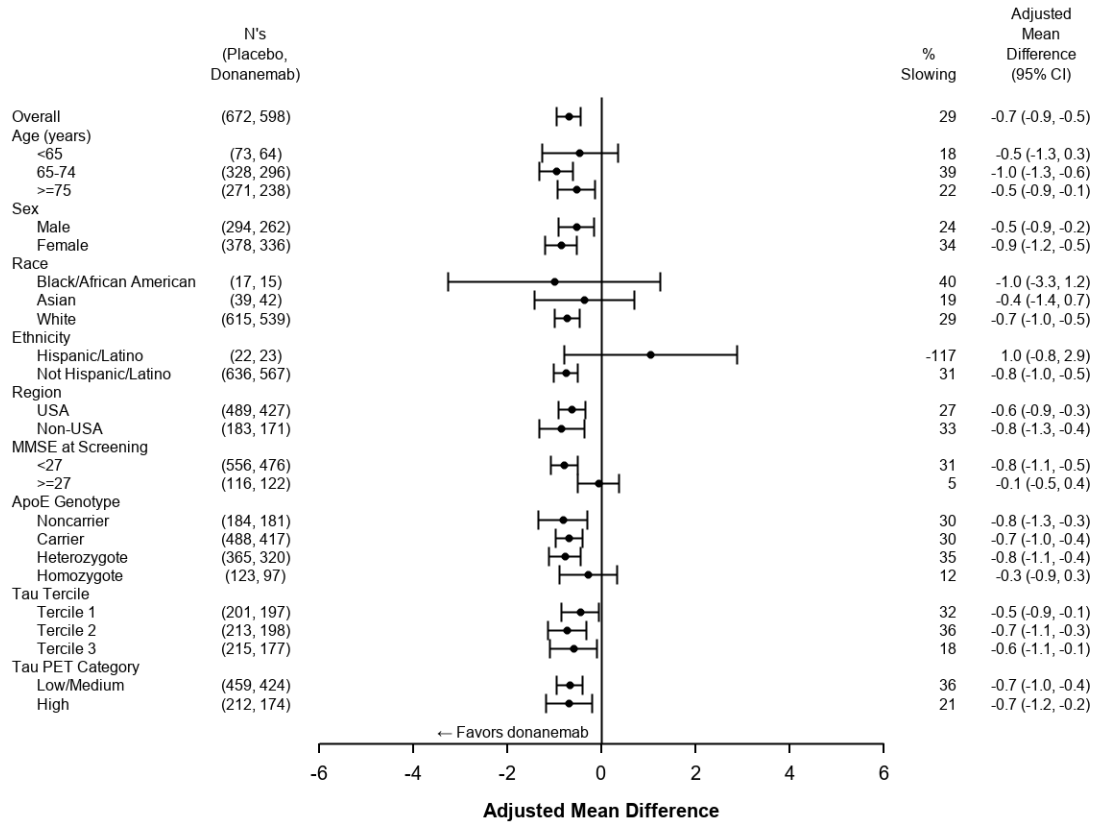
Ethnicity subgroups are based on responses from both the USA and non-USA regions.

Adjusted mean is from a natural cubic spline model (NCS2) that adjusted for NCS basis expansion terms, basis expansion terms*treatment, subgroup*treatment, subgroup*basis expansion terms, and subgroup*basis expansion*treatment, baseline age, baseline concomitant AchEI or memantine use, pooled investigator, and baseline tau PET category.

Percentage slowing: the difference of NCS2 estimates of mean change from baseline between treatment groups at Week 76 divided by the NCS2 estimate of mean change from baseline value of the placebo group.

Abbreviations: AchEI, acetylcholinesterase inhibitor ApoE, apolipoprotein E; CI, 95% confidence interval; iADRS, integrated Alzheimer's Disease Rating Scale; MMRM, mixed model with repeated measures; MMSE, Mini-mental State Examination; N, number of participants who have a baseline and Week 76 efficacy score; PET, positron emission tomography; SUVR, standard uptake value ratio

Figure 5. Subgroup Analyses for CDR-SB Change From Baseline at Week 76, Study AACI



Source: Statistical Analyst.

ApoE genotype (number of E4 alleles): Noncarrier (0), heterozygote (1), homozygote (2).

Tau tertile: Tertile 1 (SUVR <33 percentile), tertile 2 (SUVR 33-67 percentile), tertile 3 (SUVR >67 percentile).

Ethnicity subgroups are based on responses from both the USA and non-USA regions.

Adjusted mean is from the MMRM that adjusted for visit, visit*treatment, baseline CDR-SB score, baseline score*visit, baseline age, baseline concomitant AchEI or memantine use, pooled investigator, and baseline tau PET category.

Percentage slowing: the difference of MMRM estimates of mean change from baseline between treatment groups at Week 76 divided by the MMRM estimate of mean change from baseline value of the placebo group.

Abbreviations: AchEI, acetylcholinesterase inhibitor; ApoE, apolipoprotein E; CDR-SB, Clinical Dementia Rating – Sum of Boxes; CI, confidence interval; MMRM, mixed model with repeated measures; MMSE, Mini-mental State Examination; N, number of participants who have a baseline and Week 76 efficacy score; PET, positron emission tomography; SUVR, standard uptake value ratio

3.2.1.5.1 Tau Pathology

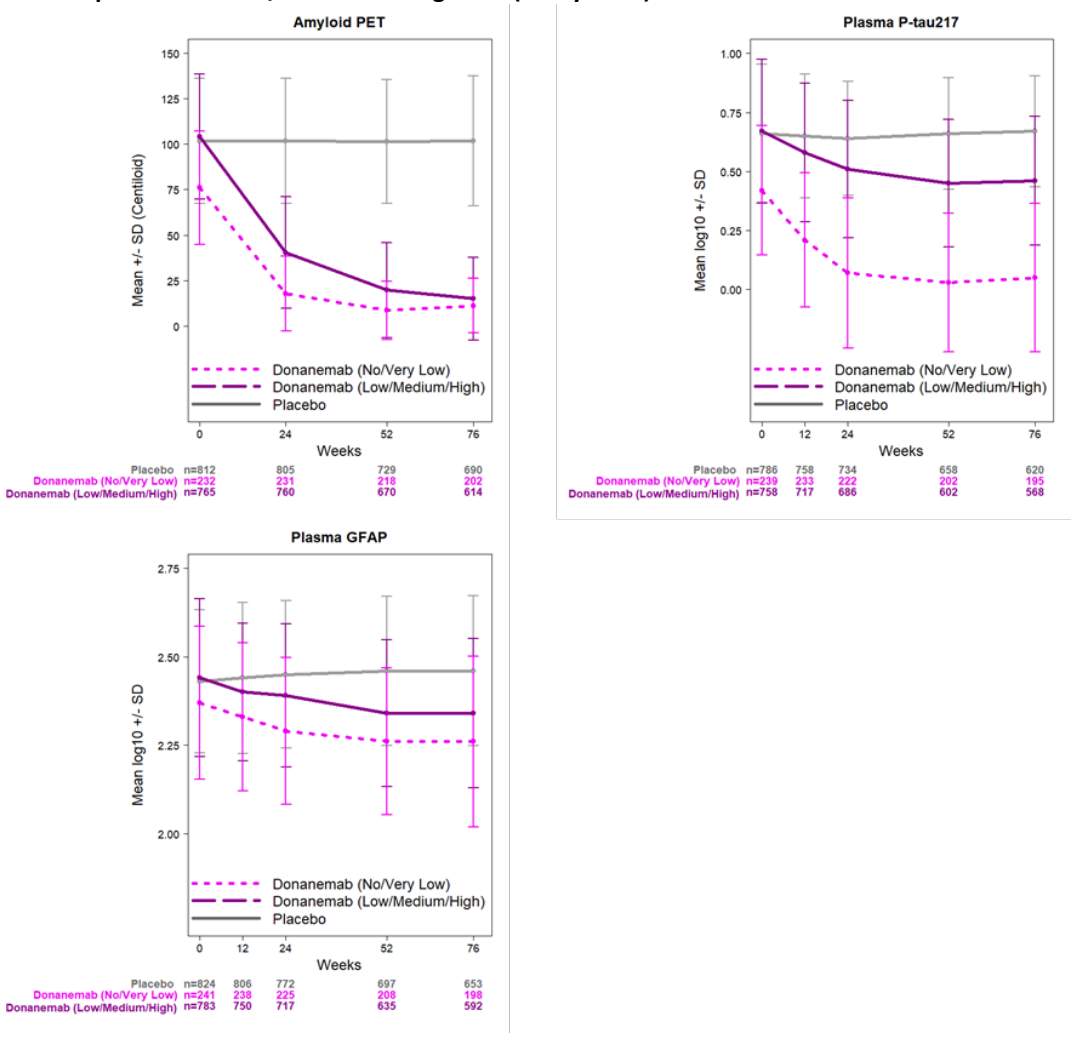
Further consideration of efficacy across the spectrum of baseline tau levels is relevant because tau PET imaging was used as an enrichment strategy in Study AACI. The Applicant does not propose a requirement for confirmation or quantification of tau pathology in the prescribing information despite excluding participants with no or very low tau from the controlled portion of Study AACI and prioritizing a low/medium tau population in the statistical analysis.

The decision to exclude participants with no or very low tau from Study AACI was based on research conducted by the Applicant demonstrating that participants with nonadvanced patterns of tau deposition were less likely to exhibit disease progression as measured by CDR-SB over an 18-month period (Lu et al. 2021). Accordingly, simulations suggested substantially greater statistical power in studies enrolling participants with more advanced tau deposition (Qian et al. 2017). Therefore, tau burden served as a prognostic biomarker to reduce the number of nonprogressors enrolled in the

studies, and exclusion of participants with no or very low tau was primarily a statistical consideration to decrease the sample size and increase the ability to detect a change during the 18-month duration of the study.

Although there is no efficacy data on clinical outcome assessments in participants with no or very low tau, there are biomarker data from 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 6).

Figure 6. Biomarker Results in Participants With No or Very Low Tau (Study AACI Safety Addendum) Compared to Participants With Low/Medium or High Tau (Study AACI)



Source: adgfap.xpt, adept.xpt, adptau.xpt, and adsl.xpt in a November 21, 2023 regulatory response; created by the Reviewer.

Data suggest that the degree of tau pathology is related to symptom severity and stage of disease, and therefore, is generally associated with a greater degree of neurodegeneration (Ossenkoppele et al.

2016). Therefore, it can be reasonably expected that patients with higher tau burden have a greater extent of neurodegeneration, and the potential for benefit may be more limited in this population compared to patients with low tau burden. Patients with low tau burden may be more likely to benefit from anti-amyloid therapy, but due to the slower rate of their disease progression, the time needed to manifest that treatment effect may be much longer than the 18-month duration of a clinical study such as Study AACI. The primary results of Study AACI in the low/medium and overall populations appear to support the expectation of a larger magnitude of treatment effect (% slowing) in patients earlier in the disease. The prespecified subgroup analyses by baseline tau tercile (Figure 4 and Figure 5) also suggest that a treatment effect was observed across the range of baseline tau levels included in Study AACI, including in participants with high tau levels. The Applicant also performed post hoc MMRM analyses to explore the relationship between tau levels and iADRS (separately CDR-SB) at Week 76. There was no trend for treatment difference in iADRS over the range of tau SUVR and an increasing treatment difference for CDR-SB with increasing baseline tau. However, greater percent slowing for both outcomes was estimated with decreasing baseline tau levels over the range of tau SUVR in the study.

3.2.1.6 Dose Cessation

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%, 42%, and 60%, respectively. Efficacy data from participants who had their dose switched to placebo during the study are inadequate to draw conclusions regarding persistence of clinical benefit due to the relatively short off-treatment period and the lack of an appropriate comparator group. The Applicant assumed that cessation of donanemab dosing once brain amyloid on PET was reduced beyond a specific threshold would not adversely affect clinical outcomes. Although this assumption is reasonable, it was not verified by including an arm with continuous donanemab dosing. There is also uncertainty regarding the optimal Centiloid threshold value for dose cessation. Data from the ongoing long-term extension portion of the study may provide insight into the persistence of effect.

Using data from patients who completed active treatment based on amyloid imaging, modeled amyloid levels began to increase with a mean rate of 2.8 Centiloids/year. The potential need for re-initiation of donanemab based on re-accumulation of amyloid remains uncertain.

3.2.2 Efficacy Results for AACG

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 the 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).

3.2.3 Efficacy Summary

Overall Efficacy

The Applicant submitted the results of Study AACI (during the placebo-controlled period) as the primary evidence of effectiveness. Study AACI was a large, multicenter study that demonstrated donanemab, as compared to placebo, reduced the change from baseline on the primary endpoint of iADRS. Although the Agency had disagreed with the use of iADRS as the primary endpoint, the statistically significant results of iADRS were supported by statistically significant results of its two component scores ADAS-Cog 13 (−1.3; 95% CI −2.1, −0.6, p<0.001) and ADCS-iADL (1.7; 95% CI 0.8, 2.6, p<0.001) in the overall population. The phase 2 study AACG's statistically significantly result for iADRS (3.2; 95% CI 0.1, 6.3; p=0.04) further supports the efficacy of donanemab.

The findings on iADRS were supported by the statistically significant results of CDR-SB. CDR-SB is an integrated scale that meaningfully assesses both daily function and cognitive effects and any increment of change on an individual domain of the CDR-SB (e.g., a change of at least 0.5) is considered to be clinically meaningful for an individual patient. Donanemab treatment demonstrated a statistically significant reduction in decline on CDR-SB change from baseline at Week 76 compared to placebo in the overall population (−0.7; 95% CI −1.0, −0.5; p<0.001). Further, the meaningfulness of the change is supported by statistically significant changes in cognition on the ADAS-cog and in daily function on the ADCS-iADL scale.

The treatment effect in Study AACI is supported by favorable results for CDR-SB and iADRS across the prespecified subgroups of interest defined by demographic and baseline disease characteristics. Brain Aβ measured by PET was significantly reduced in a time-dependent manner.

Efficacy in Tau Subgroups

Donanemab is an anti-amyloid antibody and, as such, does not require the presence of tau to exert its intended pharmacologic effect. The sequence of pathologic events is complex, but in general, brain amyloid accumulates before abnormal tau, and increased brain amyloid is directly associated with subsequent tau accumulation and neurodegeneration. Aggregated forms of amyloid beta can also be directly toxic to synapses and neurons. Therefore, there is no a priori reason to believe that a certain level of tau needs to be present for donanemab to be effective. On the contrary, current efforts, including an ongoing study with donanemab, are focused on intervening even earlier in the disease when tau levels are expected to be minimal.

It is also important to note that a negative tau PET scan with flortaucipir does not preclude the presence of tau pathology. The flortaucipir prescribing information[1] notes that performance for detecting tau pathology may be lower in patients in earlier stages of the pathologic spectrum, such as patients enrolled into Study AACI. Furthermore, neuropathogenic assessment has demonstrated that most symptomatic, amyloid positive patients also have some degree of tau pathology (Serrano-Pozo et al. 2013). Therefore, the underlying pathophysiology of the disease is not anticipated to be substantially

[1] See the Tauvid prescribing information at https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/212123s031lbl.pdf

different between symptomatic amyloid-positive patients with no or very low tau on PET compared to those with higher levels of tau on PET.

Higher levels of tau on PET imaging were used as a strategy to enrich for participants who were more likely to progress during the 18-month study. Participants 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 participants 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. However, whether the reduction in amyloid plaque in patients with no or minimal tau has the same effect on clinical endpoints has not been established. As further described in the Safety Issues section, there were no notable differences in safety between individuals with very low or no tau and individuals with higher tau burden. Based on these considerations, it may be reasonable to generalize the efficacy results from the population studied in Study AACI across the spectrum of tau burden, including patients with very low or no tau.

Dose Cessation

Donanemab dosing in Study AACI was stopped once amyloid levels were reduced below a certain quantitative threshold on PET imaging. Although participants appeared to show benefit compared to the overall placebo arm after dosing was stopped, there is not an adequate comparator group and there is no information on outcomes in similar participants if they had continued dosing. There remains uncertainty regarding the optimal treatment regimen for monoclonal antibodies targeting aggregated amyloid once amyloid levels have been reduced to a level that corresponds with a negative visual read on PET.

3.3 Safety Issues

The main safety issues associated with the use of donanemab were ARIA, intracerebral hemorrhage, Infusion-related reactions and hypersensitivity, and in addition, there was an imbalance in deaths in the donanemab arm compared to placebo.

Monoclonal antibodies directed against aggregated forms of beta amyloid, including donanemab, can cause ARIA, classified as ARIA-E, which can be observed on MRI as brain edema or sulcal effusions, and ARIA with hemosiderin deposition (ARIA-H), which includes microhemorrhage and superficial siderosis. Microhemorrhage and superficial siderosis, as well as mild focal edema, can occur spontaneously in patients with AD in the absence of treatment with amyloid targeting therapies and may be related to underlying amyloid burden or CAA; these are usually observed as incidental findings on MRI. In the setting of treatment with monoclonal antibodies directed against aggregated forms of beta amyloid, ARIA-H generally occurs in association with an occurrence of ARIA-E. ARIA-H of any cause (sporadic or drug related) and ARIA-E can occur together. ARIA is usually asymptomatic, although serious and life-threatening events, including seizure and status epilepticus, rarely can occur. When present, reported symptoms associated with ARIA may include headache, confusion, visual changes, dizziness, nausea, and gait difficulty. Focal neurologic deficits may also occur. Symptoms associated with ARIA usually resolve over time. The risk of ARIA, including symptomatic and serious ARIA, is increased in ApoE ε4 homozygotes. In addition to ARIA, intracerebral hemorrhages greater than 1 cm in diameter have

occurred in patients treated with this class of drugs, including donanemab. An increased risk of ARIA-E and ARIA-H has been observed in donanemab-treated patients with pretreatment microhemorrhage and/or superficial siderosis. The use of antithrombotic medication, particularly anticoagulation or thrombolytic therapy, may increase the risk for cerebral hemorrhage in patients taking this class of drugs. Class labeling currently describes ARIA, including the increased risk in ApoE ε4 homozygotes, in a boxed warning and provides monitoring and dose management guideline in the Warnings and Precautions Section 5.1 and in Section 2.3.

3.3.1 Sources of Data for Safety

The primary source of data for assessment of safety in the present submission is the 76-week randomized, placebo-controlled period of Study AACI, and its open label extension, in participants with mild cognitive impairment or mild dementia due to AD.

AACI Study Addendum and the two open-label studies, AACH Part B and AACN-Dona Cohort, were pooled with donanemab-treated subjects from Studies AACG and AACI (placebo-controlled and long-term extension periods) to create an all-donanemab-treated pool.

The sources of data for the all-donanemab pool are shown in Table 9.

Table 9. All-Donanemab Pool

Study	Type of Study	Treatment Duration
AACG	Randomized, double-blind, placebo controlled	72 weeks
AACH Part B (ongoing)	Open-label, follow-on study for subjects who received placebo in Study AACG	Up to 48 weeks
AACI	Placebo controlled, randomized, double blind	Up to 72 weeks
AACI Long term extension (ongoing)	Double-blind long-term extension for participants completing the placebo-controlled period	Up to 72 weeks
AACI Safety Addendum (ongoing)	Direct enrollment, open label study addendum	Up to 72 weeks
AACN Dona Cohort (ongoing)	Randomized, open-label, active comparator study	72 weeks

Source: Created by reviewer from Resubmission Integrated Summary of Safety Information (Table 5.1, Tabular Listing of Clinical Studies of Donanemab)

In Study AACI, the dosing regimen for donanemab 700 mg every 4 weeks for the first three doses, then 1400 mg every 4 weeks up to Week 72. The original protocol did not include a titration period. Based on two cases of symptomatic ARIA observed early in the study, the protocol was amended to incorporate a titration schedule of 700 mg for the first three doses.

Double-blind dose cessation of donanemab and switch to placebo was guided by amyloid PET levels measured at Week 24, Week 52, and Week 76.

3.3.2 Safety Summary

3.3.2.1 Exposures

Across the development program, 2885 participants with AD have been exposed to at least one dose of donanemab given IV, including 853 participants exposed to donanemab in the double-blind period of AACI. At the dose in the proposed labeling (700 mg every 4 weeks for three doses followed by 1400 mg every 4 weeks)[2], 1912 participants were exposed to donanemab for 6 months, 1057 participants for 12 months, and 432 participants for at least 18 months, as of the 90-day safety update. These numbers exceed the International Council for Harmonisation guidelines of 300 participants for 6 months, and 100 participants for 1 year, and provide an adequate safety database to assess the safety of donanemab.

Of note, in AACI, approximately 12% of participants randomized to donanemab had switched to placebo by Weeks 28 to 52, and approximately 32% had switched to placebo by Weeks 56 to 72. However, the safety database is adequate to support administration beyond Week 52.

3.3.2.2 Deaths

The assessment of mortality was based on the placebo-controlled period of Study AACI. The assessment included all deaths reported by Week 76 (end of the double-blind period) regardless of treatment discontinuation; this is an on-study approach to the analysis. Of the 853 participants randomized to donanemab, 221 (25.9%) discontinued the study early. Of the 874 participants randomized to placebo, 170 (19.5%) discontinued the study early. After discontinuing from the study early, vital status at Week 76 was not captured by the Applicant. This lack of vital status information collected during the conduct of AACI adds uncertainty to mortality analysis results shown in Table 10 for which there was an imbalance in deaths observed with donanemab relative to placebo. With high rates of missing vital status at Week 76 and its potential impact on the assessment of mortality, the Agency requested that the Applicant retrieve additional mortality information among participants who discontinued the AACI study prior to Week 76 and for whom the vital status was not available.

Using a third-party vendor, vital status was retrieved 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 52% (184 participants) were 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 five participants randomized to placebo died within 76 weeks. Incorporating these retrieved deaths into the deaths observed during the trial, resulted in 19 deaths on donanemab (2.3%) and 16 deaths on placebo (1.9%) that occurred within 76 weeks of randomization (Table 11). Inclusion of these retrieved deaths reduced the imbalance in deaths observed from the deaths observed during Trial AACI; however, it is worth noting that approximately 10% of subjects still have missing vital status information (data could not be obtained in some subjects due to regulatory and/or legal requirements in other countries) and the retrieved vital status information lacks information on cause of death.

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

Table 10. Mortality Assessment of the Placebo-Controlled Period of Study AACI (Safety Population); On Study

Variable	Donanemab N=853 n, (%[1])	Placebo N=874 n, (%[1])	RD (95% CI)	HR[2] (95% CI)
Mortality at 76 weeks	17 (2.2%)	10 (1.2%)	1.0% (−0.3%,2.3%)	1.80 (0.83, 3.94)
Non-ARIA mortality at 76 weeks	14 (1.8%)	10 (1.2%)	0.6% (−0.6%,1.8%)	1.49 (0.66, 3.35)

Source: DBVII Statistical Reviewer's analysis using SUBJINFO.XPT in SN161.

[1] Kaplan–Meier estimates of cumulative incidence.

[2] Hazard ratio estimate from Cox proportional hazards model without covariate adjustment.

Abbreviations: ARIA, amyloid-related imaging abnormalities; CI, confidence interval; HR, hazard ratio; N, number of participants; n, number of participants with a given variable; RD, risk difference

Table 11. Updated Mortality Assessment of the Placebo-Controlled Period of Study AACI (Safety Population); On Study

Variable	Donanemab N=853 n, (%[1])	Placebo N=874 n, (%[1])
Mortality at 76 weeks	19 (2.3%)	16 (1.9%)

Source: DBVII Statistical Reviewer's analysis using SUBJINFO.XPT in SN175.

[1] Kaplan-Meier estimates of cumulative incidence.

Abbreviations: N, number of participants; n, number of participants with a given variable

For subjects in AACI in whom a cause of death was available, these adverse events are listed in Table 12.

Table 12. Adverse Events With Fatal Outcomes in the Placebo-Controlled Period of Study AACI; On Study

Preferred Term	Placebo N=874 n	Donanemab N=853 n
Participants with adverse events with fatal outcome	10	17
Nervous system disorders		
ARIA-E	0	1
ARIA-E and ARIA-H[1]	0	1
Intracerebral hemorrhage[2]	0	1
Subarachnoid hemorrhage	0	1
Dementia Alzheimer's type	1	1
General disorders and administration site conditions		
Death[3]	1	1
Infections and infestations		
COVID-19	0	1
COVID-19 pneumonia[4]	1	1
Pneumonia	2	1
Sepsis	1	0
Gastrointestinal disorders		
Retroperitoneal hemorrhage	0	1
Metabolism and nutrition disorders		
Dehydration	0	1
Psychiatric disorders		
Completed suicide	1	2
Respiratory, thoracic and mediastinal disorders		
Pulmonary embolism	0	2
Respiratory arrest	0	1
Respiratory failure	0	1

Preferred Term	Placebo N=874 n	Donanemab N=853 n
Injury, poisoning and procedural complications		
Respiratory fume inhalation disorder	1	0
Vascular disorders		
Arteriosclerosis	1	0
Cardiac disorders		
Myocardial infarction	1	0

Source: Ninety-Day Safety Update IDB ADAE dataset.

[1] Preferred term was death. The events associated with death were ARIA-E and ARIA-H.

[2] Intracerebral hemorrhage in the setting of ARIA-E and ARIA-H, with superficial siderosis at baseline

[3] Donanemab death was one participant with a history of hypertension, hyperlipidemia, and concomitant meds including alprazolam who died in sleep with no other information available.

[4] Donanemab-treated participant with respiratory failure in the setting of COVID-19 pneumonia

Abbreviations: ARIA-E, amyloid-related imaging abnormality-edema/effusion; ARIA-H, amyloid-related imaging abnormality-microhemorrhages and hemosiderin deposits; COVID-19, coronavirus disease 2019; N, number of participants; n, number of participants with a given variable

Deaths Associated With ARIA

In the placebo-controlled period of Study AACI there were three ARIA-related deaths in the donanemab-treated group, and including one death from cerebral hemorrhage in the setting of ARIA E and ARIA H, compared to none on placebo.

In the all-donanemab pool, there was an additional death from ARIA and an additional death from intracerebral hemorrhage in the setting of ARIA E. Both of the deaths from intracerebral hemorrhage were in patients with findings consistent with cerebral amyloid angiopathy (CAA), which is a known risk factor for intracerebral hemorrhage. and in one case, the patient had symptoms mimicking stroke and was administered thrombolytic therapy.

Other Causes of Death

Other deaths in donanemab-treated patients included a thalamus hemorrhage in a patient with a history of hypertension and one death each from subarachnoid hemorrhage and blunt-force head injury in patients with falls. Other than ARIA-related deaths, the remaining deaths did not appear to be causally related to donanemab and there was no unusual grouping of deaths that would suggest a causal relationship. Additional deaths beyond the 76-week on -study period of Study AACI included death in a donanemab-treated patient with multiple fractures from unwitnessed fall 4 days after the 76-week period, cerebrovascular accident in a donanemab-treated patient after a carotid endarterectomy with death 52 days after the 76-week period, and death from malignant lung neoplasm in a placebo-treated patient 2 days after the 76-week period.

3.3.2.3 Serious Adverse Events

Serious adverse events (SAEs) occurring within 57 days of the last dose occurred more frequently in the donanemab -treated group in Study AACI and were driven by ARIA-E. SAEs occurring in at least five participants and more frequently than in placebo in Study AACI are shown in Table 13.

Table 13. Most Frequent Treatment-Emergent SAEs, Study AACI

SAE	Placebo N=874 n (%)	Donanemab N=853 n (%)
Total SAEs	124 (14)	140 (16)
ARIA--E	0	13 (1.5%)
COVID-19	4 (0.5%)	7 (0.8%)
Pneumonia	3 (0.3%)	5 (0.6%)

Source: ADAE dataset.

Abbreviations: ARIA-E, amyloid-related imaging abnormalities with edema; COVID-19, coronavirus disease 2019; N, number of participants; n, number of participants with a given SAE; SAE, serious adverse event

The incidence of SAEs in the all-donanemab pool was 14% (393/2802) and was driven by ARIA-E (1%), syncope (0.9%), pneumonia (0.6%), coronavirus disease 2019 (COVID-19) (0.6%) and fall (0.6%).

3.3.2.4 Discontinuations

In the placebo-controlled period of Study AACI, 30% of donanemab-treated participants discontinued treatment compared to 20% of placebo-treated participants. Adverse events led to treatment discontinuation in 13% of donanemab-treated participants compared to 4% on placebo. Infusion-related reactions and ARIA-E were the most frequent adverse events leading to treatment discontinuation. Of note, in AACI, 26% (226/853) donanemab participants discontinued the study compared to 20% (174/874) on placebo, resulting in incomplete vital status. The timing of treatment discontinuation and of study discontinuation is shown in Section 5.1.

3.3.2.5 Treatment Emergent Adverse Events

The incidence of treatment-emergent adverse events (TEAEs) within 57 days of the last dose in AACI was 89% in the donanemab arm and 82% in the placebo arm. A summary of TEAEs in Study AACI is shown in Table 14. The most frequently reported TEAEs on donanemab were ARIA-H microhemorrhage, ARIA-E, and superficial siderosis. Of note, these TEAEs do not include individual TEAEs associated with events of ARIA.

Table 14. Adverse Events Reported in at Least 5% of Participants Treated With Donanemab and at Least 2% Greater Than Placebo in the Placebo-Controlled Period of Study AACI

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

Source: IDB ADAE dataset submitted in the 90-Day Safety Update.

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

[2] The term headache does not include headache associated with ARIA

Abbreviations: ARIA, amyloid-related imaging abnormalities; ARIA-H, amyloid-related imaging abnormalities with hemosiderin deposition; MRI, magnetic resonance imaging; N, number of participants; n, number of participants with a given AE; TEAE, treatment -emergent adverse event

In the all-donanemab pool, the most common (≥10%) TEAEs were: ARIA-H (26%), ARIA-E (20%), COVID-19 (13%), headache (11%), and fall (10%).

3.3.2.6 Other Important Safety Issues

3.3.2.6.1 Amyloid-Related Imaging Abnormalities

Incidence

Monoclonal antibodies directed against aggregated forms of beta amyloid, including donanemab, can cause ARIA. Table 15 shows the incidence of ARIA events, on treatment or within 57 days of the last dose of study drug, in Study AACI. ARIA-E or ARIA-H may occur in isolation or concurrently. ARIA-H frequently occurs in association with an occurrence of ARIA-E.

Table 15. Incidence of Treatment-Emergent ARIA or Cerebral Hemorrhage in Study AACI

Variable	Placebo N=874 n (%)	Donanemab N=853 n (%)
ARIA	122 (14)	307 (36)
ARIA-E	17 (2)	201 (24)
Symptomatic ARIA-E[1]	0	52 (6)
ARIA-H	111 (13)	263 (31)
Isolated ARIA-H	105 (12)	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)

Source: Incidence of ARIA is based on analyses using the MRI dataset. The incidence of intracerebral hemorrhage >1 cm is based on analyses using the combined adverse event, MRI datasets, and a review of narratives.

[1] Symptoms of ARIA-H were not collected in Study AACI.

Abbreviations: ARIA, amyloid-related imaging abnormalities; ARIA-E, amyloid-related imaging abnormalities with edema; ARIA-H, amyloid-related imaging abnormalities with hemosiderin deposition; MRI, magnetic resonance imaging; N, number of participants; n, number of participants with a given variable

Among participants in the all-donanemab pool who had not received donanemab in a previous study (n=1818), the incidences of ARIA (30%), ARIA-E (19%), and ARIA-H (25%) were similar to those in Study AACI. In the all -donanemab pool (n=2802), the incidences of ARIA overall (32%), ARIA-E (20%), and ARIA-H (26%) were similar to those in Study AACI alone.

The Applicant identified the presence of two to four microhemorrhages at baseline or the presence of one 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.

Intracerebral hemorrhage greater than 1 cm occurred on treatment or within 57 days of the last dose of study drug in 0.5% of participants on donanemab and in 0.2% on placebo. The four participants on donanemab had risk factors for cerebral hemorrhage including an ApoE ε4 allele in three of the participants and findings consistent with cerebral amyloid angiopathy including superficial siderosis prior to the event.[3] Four additional participants with cerebral hemorrhage greater than 1 cm in all - donanemab pool had risk factors including thrombolytic therapy in one participant, and superficial

[3] One participant had superficial siderosis on MRI at baseline, and elevated blood pressure at the time of the event and on two previous visits. One participant had a finding of superficial siderosis prior to the event of cerebral hemorrhage in the same area as the cerebral hemorrhage and continuing at the time of the event, and was on the antiplatelet drug prasugrel for carotid artery stenosis. One participant 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; three microhemorrhages; superficial siderosis in right frontal at the time of the event. One participant, with aspirin use prior to the event, had baseline superficial siderosis and presence of white matter disease with beginning of confluence of lesions.

siderosis and/or an ApoE ε4 allele in the other three participants. The incidence of cerebral hemorrhage >1 cm in all-donanemab pool was 0.3% (8/2802). One additional participant, homozygous for ApoE ε4, on aspirin 325 mg daily, had cerebral hemorrhage 78 days after the only dose in the setting of severe ARIA E that began 22 days after the only dose, ARIA-H microhemorrhage and superficial siderosis.

ApoE ε4 Genotype

ApoE ε4 homozygotes have been previously shown to have an increased incidence of ARIA compared to heterozygotes and noncarriers in participants taking monoclonal antibodies directed against aggregated forms of beta amyloid. In the placebo-controlled portion of Study AACI, 17% (143/853) of participants in the donanemab group were ApoE ε4 homozygotes, 53% (452/853) were heterozygotes, 30% (255/853) were noncarriers, and in three participants 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 16. ApoE ε4 has been associated with increased risk of intracerebral hemorrhage (Marini et al. 2019). Limited data do not allow for a conclusion regarding risk of intracerebral hemorrhage in ApoE ε4 carriers on donanemab.

Table 16. Incidence of ARIA and Cerebral Hemorrhage Greater Than 1 cm by ApoE ε4 Genotype in Participants Exposed to Donanemab in Study AACI (MRI Dataset)

	Noncarriers		Heterozygote		Homozygote	
	Placebo N=250	Donanemab N=255	Placebo N=474	Donanemab (N=452)	Placebo N=146	Donanemab N=143
Variable	n (%)	n (%)	n (%)	n (%)	n (%)	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 >1 cm	0	1 (0.4)	1 (0.2)[1]	3 (0.7)	0	0

Source: The incidence of ARIA is based on analyses using the MRI dataset. The incidence of intracerebral hemorrhage > 1 cm is based on analyses using the combined adverse event, MRI datasets, and a review of narratives.

[1] One additional placebo participant had unknown ApoE genotype.

Abbreviations: ApoE, apolipoprotein E; ARIA, amyloid-related imaging abnormalities; ARIA-E, amyloid-related imaging abnormalities with edema; ARIA-H, amyloid-related imaging abnormalities with hemosiderin deposition; MRI, magnetic resonance imaging; N, number of participants; n, number of participants with a given variable

Symptoms

The majority of ARIA cases in Study AACI were asymptomatic, consistent with other drugs in this class. In AACI, the incidence of symptomatic ARIA-E was 6% (52/853) in participants treated with donanemab compared to none in the placebo group. Of the 52 donanemab-treated participants 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 in participants with ARIA-E on donanemab in Study 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 participants, 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 Study 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 participants. Symptomatic ARIA was not categorized by seriousness in the database.

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

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

Radiographic Severity
Among the 853 participants treated with donanemab in Study 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%. Similar findings for maximum radiographic severity were observed in the all -donanemab pool.

Timing of ARIA Events
Routine Safety MRIs to monitor for ARIA were to be performed to prior to the second, fourth, seventh, and fourteenth doses and approximately 4 weeks after the last dose in Study AACI.

In Study AACI, 58% of participants with ARIA had a first episode of ARIA E prior to the fourth dose and the majority of ARIA-E radiographic events (89%) occurred prior to the seventh dose. Additional ARIA-E events continued to occur as late as after the nineteenth dose. Similar timing was observed in the all-donanemab pool. First events of ARIA-H occurred with similar timing: Approximately 41% prior to the fourth dose, approximately 71% prior to the seventh dose, and 93% prior to the fourteenth dose, with additional events as late as after the nineteenth dose.

In Study AACI, a first event of ARIA-E in participants on donanemab resolved by Week 12 after detection in 63% (126/201) of participants, by Week 20 in 80% (160/201), and in 83% by the end of the study; median time to resolution was 57 days (15 to 287 days). Time to resolution in the all-donanemab pool was similar to that observed in Study AACI.

In Study AACI, approximately 24% (48/201) of participants with ARIA-E on donanemab had more than one treatment-emergent event of ARIA E. Thirty-five participants (17%) had two events, and 13 participants (6.5%) had more than two events. Although there is experience in participants having more than one 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 participants with ARIA-E). There is limited experience with donanemab in continued dosing through symptomatic, radiographically mild ARIA-E.

Antithrombotic Use
In Study AACI, antithrombotic use was allowed. The protocol excluded patients with more than four microhemorrhages, more than one area of superficial siderosis, any macrohemorrhage (size not defined), or severe white matter disease at screening.

In Study AACI, participants 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 participants who received no antithrombotic (29%, 148/504). There was no difference in incidence of ARIA-H in participants with concomitant use of anticoagulant or aspirin greater than 81 mg daily or a combination compared to those using less than or equal to 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 participants exposed to antithrombotic medication other than low dose aspirin.

Among participants treated with donanemab in Study AACI, those who received antithrombotic medication within 30 days prior to an intracerebral hemorrhage event had a slightly higher incidence of cerebral hemorrhage (0.6%, 2/349) than those who did not receive an antithrombotic (0.4%, 2/504). The limited number of cerebral hemorrhage events on placebo, with none on antithrombotic medication, preclude a comparison with the risk of antithrombic use in placebo.

Among donanemab-treated participants, the majority of exposures to antithrombotic medications in Study AACI were to aspirin less than or equal to 81 mg (59%, 206/349). Approximately 10% of donanemab-treated participants were exposed to anticoagulation. The small number of cerebral hemorrhages and small numbers exposed to antithrombotics and anticoagulants, as well ask other risk factors for cerebral hemorrhage noted above, limit interpretation of these results regarding intracerebral hemorrhage in patients exposed to donanemab. However, because intracerebral hemorrhages greater than 1 cm in diameter have been observed in participants taking donanemab, class labeling will be used if donanemab is approved, 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.

Of note, one cerebral hemorrhage occurred after thrombolytic use (tenecteplase) for symptoms mimicking stroke in the setting of ARIA-E. 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. This will be addressed in labeling if donanemab is approved.

Seizures

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 AD may be at increased risk for seizures (Pandis and Scarmeas 2012). In Study AACI, seizures occurred both independent of ARIA as well as in the setting of ARIA. In the placebo-controlled period of Study AACI, seizures occurred in 1.2% (10/853) in participants 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; six of those seizures were reported as a symptom of ARIA-E (0.2%, 6/2802).

SAEs of seizure occurred in 0.4% in donanemab versus 0.1% in placebo in the placebo-controlled period of Study AACI. Overall, in the all-donanemab pool, SAEs of seizure occurred in 0.2% (7/2802). SAEs of seizure occurred in the setting of hemorrhagic stroke, ARIA-E, or occurred in the setting of diabetic ketoacidosis, and metabolic encephalopathy/COVID-19.

3.3.2.6.2 Infusion Reactions and Hypersensitivity Reactions

In the placebo-controlled period of Study AACI, 9% (74/853) of donanemab participants versus 0.5% (4/874) of placebo participants had at least one 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 participant (0.1%) had an infusion reaction categorized as a SAE after administration of donanemab. In

Study AACI, the majority (70%, 52/74) of infusion reactions occurred within the first four infusions of donanemab. Infusion-related reactions led to treatment discontinuation in 4% (31/853) of donanemab treated participants and none on placebo. Similar findings were observed in the all-donanemab pool. The incidence of subsequent infusion-related reactions after a first event on donanemab was similar with and without preventative medication. Similarly, the incidence of subsequent infusion-related reactions was no different whether or not infusions were slowed.

Symptoms associated with infusion reactions in Study AACI included chills, erythema, nausea/vomiting, dyspnea, sweating, elevated blood pressure, headache, chest pain, and low blood pressure. Three participants had increases in blood pressure in the setting of infusion reactions in Study AACI: one participant with a history of hypertension and hyperlipidemia who had myocardial infarction with blood pressure of 217/117 mm Hg within 5 minutes of starting the infusion (prior to the infusion was 150/80 mm Hg); one participant with angina with blood pressure of 168/108 mm Hg (versus 139/78 mm Hg predose) and with past medical history of coronary artery disease and hypertension; and one participant with no known risk factors who had respiratory distress with blood pressure of 142/90 mm Hg, heart rate 118 bpm, and oxygen saturation of 82% (versus predose blood pressure of 122/76 mm Hg; heart rate 79 bpm).

Hypersensitivity events other than infusion related reactions occurred in approximately 3% of donanemab-treated participants and 0.7% of placebo-treated participants in the placebo-controlled period of Study AACI. In Study AACI, anaphylactic reaction occurred in 0.4% (3/853) participants on donanemab and none in placebo. Angioedema was reported in 1.2% of donanemab-treated participants versus 0.5% on placebo.

3.3.2.6.3 Safety Profile in Patients With No or a Very Low Tau Burden

Participants with no or very low tau burden, as assessed by PET, although included in the Safety Addendum of Study AACI, were excluded from the placebo-controlled period of Study AACI that included patients with low/medium or high tau burden. There were no notable differences in safety between donanemab-treated no/very low tau participants in the Safety Addendum (n=250) and donanemab-treated participants in the placebo-controlled period of AACI (n=853). These findings are limited by the relatively small population with no/very low tau burden.

3.3.2.7 Safety Conclusion

In summary, the main safety signals associated with the use of donanemab are ARIA, cerebral hemorrhage, and infusion-related reactions and hypersensitivity. The safety findings are generally consistent with findings associated with the class of monoclonal antibodies directed against aggregated forms of beta amyloid.

The presence of ApoE ε4 increases the risk of ARIA in a dose-dependent manner. Interpretation of the risk of ARIA-H or cerebral hemorrhage in the presence of concomitant use of antithrombotic medication is limited by small numbers of cerebral hemorrhages and small numbers of participants exposed to antithrombotics and anticoagulants, as well as confounding factors that include the presence of ApoE ε4 allele, presence of superficial siderosis and microhemorrhages, and possible cerebral amyloid angiopathy.

The role for an interaction between donanemab and underlying risk factors for cerebral hemorrhage, such as ApoE ε4 alleles or underlying CAA, has not been determined. There is a high background prevalence of CAA in participants with Alzheimer's disease, and a lack of definitive criteria for diagnosing

CAA. This results in inability to compare the risk of cerebral hemorrhage in donanemab-treated participants with or without CAA and leads to substantial uncertainty in the ability to make any recommendations regarding use of donanemab in participants with CAA. However, if donanemab is approved, risk factors for cerebral hemorrhage, including concomitant anticoagulant therapy or MRI findings suggestive of CAA will be identified in labeling.

An imbalance in deaths in donanemab-treated participants compared to placebo treated participants cannot be completely explained by deaths due to ARIA or cerebral hemorrhage. Other than ARIA-related deaths, the deaths did not appear to be causally related to donanemab and there was no unusual grouping of deaths that would suggest a causal relationship.

There were adverse events associated with infusion reactions and hypersensitivity including anaphylaxis.

The risks can be described in the prescribing information, including a boxed warning concerning ARIA, recommendations regarding MRI monitoring, and a contraindication for serious hypersensitivity reactions.

3.3.3 Risk Mitigation

If donanemab is approved, it is anticipated that the following risks and mitigation strategies will be described in labeling:

- The risks of ARIA and cerebral hemorrhage, including the increased risk in ApoE ε4 homozygotes, would be described in the boxed warning and in Warnings and Precautions, as class labeling
- The risks of hypersensitivity reactions and of infusion-related reactions would be described in Warnings and Precautions.
- Recommendations for MRI monitoring consistent with the timing of ARIA events in the clinical studies with additional MRI evaluation performed in response to symptoms.
- Description of risk factors for cerebral hemorrhage, including concomitant anticoagulant therapy or MRI findings suggestive of CAA.
- A statement that ARIA-E can cause focal neurologic deficits that can mimic an ischemic stroke, and clinicians should consider whether such symptoms could be due to ARIA-E before giving thrombolytic therapy in a patient taking donanemab.

If donanemab is approved, it is anticipated that the following postmarketing risk mitigation strategies will be requested:

- Postmarketing pharmacovigilance:
  - Expedited reporting of any deaths in ongoing studies and of deaths resulting from cerebral hemorrhage greater than 1 cm in size in the postmarketing setting.
  - Characterize the risk of ARIA associated with the use of donanemab, including evaluation of intracerebral hemorrhage in patients with pre-existing risk factors for bleeding, including concomitant medications that could increase the risk for bleeding.
- Postmarketing requirements to further characterize ARIA and associated symptoms, intracerebral hemorrhage >1 cm in size, as well as seizures, anaphylaxis, and death, using registry data.
- A postmarketing commitment for development of a test for ApoE ε4 genotype.

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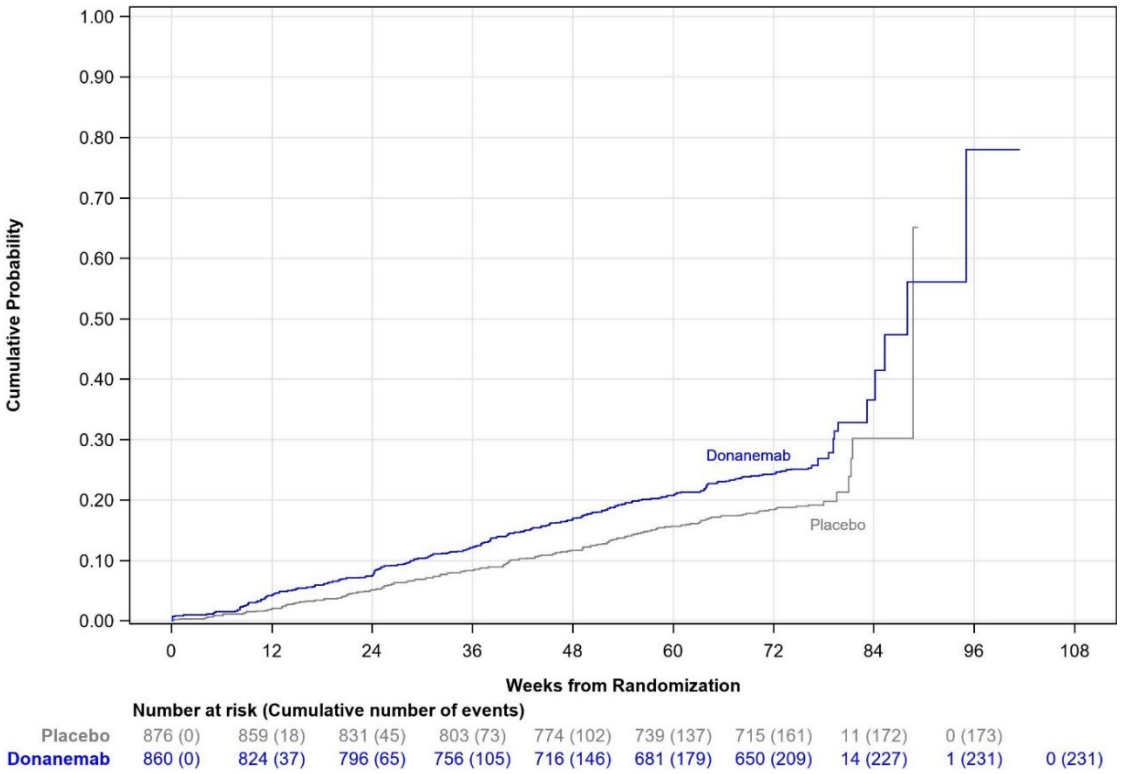
5 Appendix

5.1 Participant Disposition

Figure 7. Time to Study Discontinuation, Study AACI

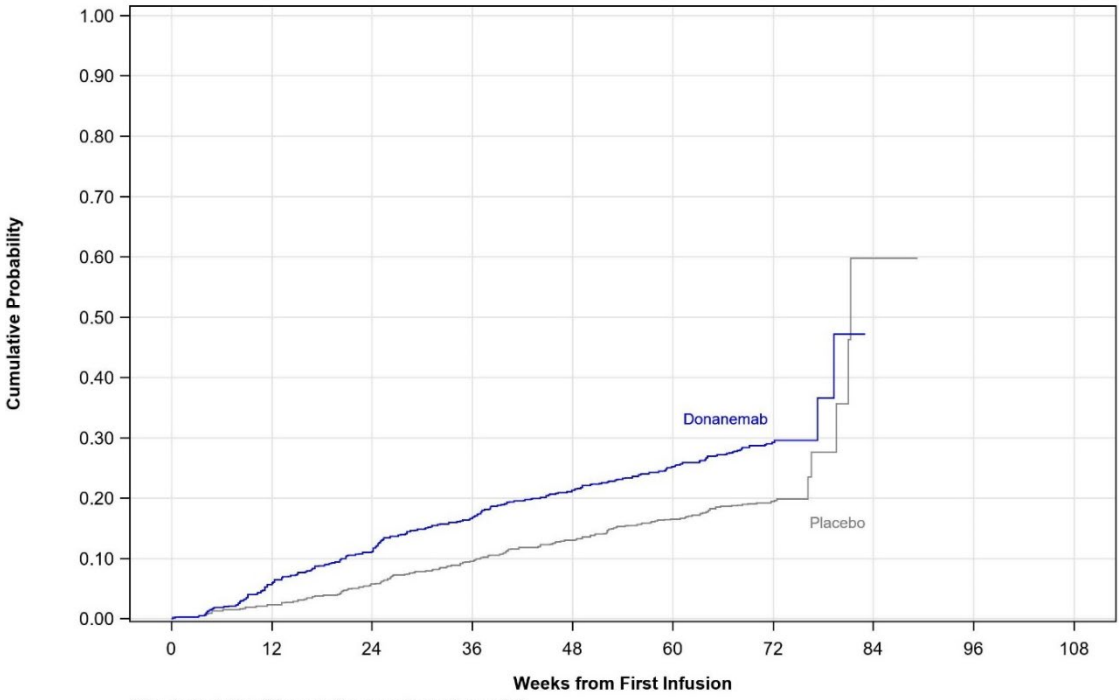


Number at risk (Cumulative number of events)

Placebo	876 (0)	859 (18)	831 (45)	803 (73)	774 (102)	739 (137)	715 (161)	11 (172)	0 (173)	
Donanemab	860 (0)	824 (37)	796 (65)	756 (105)	716 (146)	681 (179)	650 (209)	14 (227)	1 (231)	0 (231)

Source: Statistical Analyst.

Figure 8. Time to Treatment Discontinuation, Study AACI



Number at risk (Cumulative number of events)

Placebo	874 (0)	852 (20)	821 (50)	788 (83)	757 (113)	725 (144)	574 (169)	1 (176)	0 (176)
Donanemab	853 (0)	804 (50)	757 (95)	710 (143)	670 (181)	632 (214)	503 (248)	0 (252)	

Source: Statistical Analyst.

The starting numbers at risk comprised participants who had at least one dose of treatment.