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APPLICATION NUMBER:

761248Orig1s000

CLINICAL REVIEW(S)

Clinical Review
Kevin Krudys, PhD
BLA 761248 Resubmission
Kisunla (Donanemab)

CLINICAL REVIEW

Application Type	BLA (resubmission)
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Division/Office	Division of Neurology 1/Office of Neurology
Reviewer Name(s)	Kevin Krudys, PhD
Review Completion Date	06/27/2024
Established/Proper Name	Donanemab
(Proposed) Trade Name	Kisunla
Applicant	Eli Lilly and Company
Dosage Form(s)	Solution for injection
Applicant Proposed Dosing Regimen(s)	700 mg as an infusion every four weeks for the first three doses, followed by 1400 mg every four weeks. Consider stopping treatment once amyloid plaque is cleared.
Applicant Proposed Indication(s)/Population(s)	Treatment of Alzheimer's disease
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Treatment of Alzheimer's disease

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Glossary

A β	amyloid beta
AC	advisory committee
AD	Alzheimer's disease
ADA	anti-drug antibody
ADAS-Cog	Alzheimer's Disease Assessment Scale – Cognitive Subscale
ADCS-ADL	Alzheimer's Disease Cooperative Study – Activities of Daily Living
ADCS-iADL	Alzheimer's Disease Cooperative Study – instrumental Activities of Daily Living subscale
AE	adverse event
ApoE	apolipoprotein E
ARIA	amyloid-related imaging abnormalities
ARIA-E	amyloid-related imaging abnormalities-edema
ARIA-H	amyloid-related imaging abnormalities-hemorrhage
BACE	β -site amyloid precursor protein cleaving enzyme
BLA	biologics license application
BRF	Benefit Risk Framework
CDER	Center for Drug Evaluation and Research
CDR	Clinical Dementia Rating
CDR-SB	Clinical Dementia Rating Sum of Boxes
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
CR	complete response
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DIAD	dominantly inherited Alzheimer's disease
DMC	data monitoring committee
DPM	disease progression model
eCTD	electronic common technical document
FDA	Food and Drug Administration
GCP	good clinical practice
GFAP	glial fibrillary acidic protein
iADRS	integrated Alzheimer's Disease Rating Scale
ICH	International Council for Harmonization
IgG1	immunoglobulin G1

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IND	Investigational New Drug Application
ISE	integrated summary of effectiveness
ITT	intent to treat
LS	least square
mITT	modified intent to treat
MMRM	mixed-effects model repeated measures
MMSE	Mini-Mental State Examination
MRI	magnetic resonance imaging
N3pG	N-terminal, third amino acid, pyroglutamate formation
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NCS	natural cubic splines
NDA	new drug application
NfL	neurofilament light chain
NIA-AA	National Institute on Aging at the National Institutes of Health and the Alzheimer's Association
NME	new molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PET	Positron Emission Tomography
PI	prescribing information or package insert
PK	pharmacokinetics
PKPD	pharmacokinetic-pharmacodynamic
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PRO	patient reported outcome
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
TEAE	treatment emergent adverse event
SUVR	standard uptake value ratio
vmRI	volumetric magnetic resonance imaging

1. Executive Summary

1.1. Product Introduction

Donanemab (previously LY3002813) is a humanized immunoglobulin G1 (IgG1) monoclonal antibody targeting brain amyloid plaque. Extracellular deposits of amyloid beta (A β) are one of two pathological hallmarks of Alzheimer's disease, along with intracellular aggregates of hyperphosphorylated tau in the form of neurofibrillary tangles. Different A β species are defined by their size and structure and include monomers, oligomers and protofibrils, and insoluble fibrils and plaques. Accumulation of A β in the brain is a defining feature of the disease that precedes neurodegeneration and clinical decline. Donanemab reduces brain A β plaque by targeting the N-terminal, third amino acid, pyroglutamate formation (N3pG) epitope that is present in brain amyloid plaques.

The applicant's proposed indication is the treatment of Alzheimer's disease in patients with either mild cognitive impairment or mild dementia stage of disease. The proposed dosing regimen is an intravenous infusion of 700 mg donanemab over approximately 30 minutes, once every four weeks for the first three doses, followed by 1400 mg every four weeks until amyloid plaque is cleared. Donanemab is available as a 350 mg/20 mL solution in a single-dose vial for intravenous infusion.

Donanemab is a new molecular entity (NME) and is not marketed in any country. The proposed proprietary name is Kisunla. The original application for accelerated approval of donanemab received a Complete Response (CR) letter on January 18, 2023, because the safety database was insufficient to adequately characterize the long-term safety of donanemab for the treatment of Alzheimer's disease. This resubmission application seeks traditional approval and includes the results of the pivotal clinical trial (Study AACI) and is also intended to address the deficiencies outlined in the CR letter.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The applicant has provided substantial evidence to support approval based on two adequate and well-controlled multicenter trials (Study AACG and Study AACI).

Study AACI is a large, multicenter, adequate and well-controlled study that demonstrated statistically persuasive and clinically meaningful benefits in cognition and function in subjects with Alzheimer's disease. In Study AACI, participants treated with donanemab demonstrated a statistically significant reduced clinical decline on the primary endpoint, the integrated Alzheimer's Disease Rating Scale (iADRS), compared to placebo, and also on the two clinical endpoints that comprise the iADRS, the Alzheimer's Disease Assessment Scale – Cognitive

Subscale 13 (ADAS-Cog 13) and the Alzheimer's Disease Cooperative Study – instrumental Activities of Daily Living subscale (ADCS-iADL). In addition, a clinically meaningful and statistically very persuasive effect was demonstrated for the Clinical Dementia Rating – Sum of Boxes (CDR-SB). The robust, compelling, and consistent results across multiple clinical outcomes and biomarkers, and across subgroups of the population, provide strong evidence for the effectiveness of donanemab for the treatment of Alzheimer's disease.

Study AACG was a smaller Phase 2 study that also demonstrated a statistically significant reduced clinical decline on the iADRS in participants treated with donanemab compared to placebo. Despite not reaching statistical significance according to the prespecified hierarchy, the estimates of the treatment effect across secondary endpoints, including CDR-SB, ADAS-Cog 13, and ADCS-iADL, were consistent with the reduction of clinical decline observed in Study AACI and provide independent substantiation of the benefits demonstrated in that study.

Brain amyloid plaque was significantly reduced in both studies and the effects on downstream biomarkers support the observations on the clinical outcome measures.

1.3. Benefit-Risk Assessment

Benefit-Risk Integrated Assessment

Donanemab is a monoclonal antibody directed against insoluble N-truncated pyroglutamate amyloid beta. The proposed indication is the treatment of Alzheimer's disease. This reviewer recommends approval based on efficacy data from two adequate and well-controlled studies that demonstrated the clinical benefit of donanemab.

Alzheimer's disease is an irreversible and progressive disease that affects memory, thinking, and behavior and is ultimately fatal. After a diagnosis of Alzheimer's disease dementia, the average survival is 4 to 8 years. Alzheimer's disease was the sixth leading cause of death in the United States in 2019. Acetylcholinesterase inhibitors (donepezil, galantamine, and rivastigmine) and the N-methyl-D-aspartate receptor antagonist memantine are approved therapies for the treatment of Alzheimer's disease, but they do not target the underlying pathology of the disease and their effects are modest and short-lived. Aducanumab and lecanemab are amyloid-beta directed antibodies that received accelerated approval and traditional approval, respectively, and are indicated for the treatment of Alzheimer's disease, specifically patients with mild cognitive impairment (MCI) or mild dementia stage of disease. There remains an urgent and unmet medical need for additional effective treatments for Alzheimer's disease, and a particular need for effective therapies to delay, halt, or reverse the pathophysiological processes that ultimately lead to the clinical deficits of Alzheimer's disease.

The applicant is seeking traditional approval based primarily on results from Study AACI, a multicenter, randomized, double-blind, placebo-controlled, parallel group study in subjects with early symptomatic Alzheimer's disease. Subjects were required to have evidence of brain amyloid and tau pathology on PET scans. The study included a screening period of up to 7 weeks, a 76-week placebo-controlled treatment period, and an immunogenicity and safety follow-up period of 44 weeks. Subjects were randomized to placebo or donanemab treatment in a 1:1 ratio in the placebo-controlled period. The primary efficacy endpoint was change in the integrated Alzheimer's Disease Rating Scale (iADRS) score from baseline to 76 weeks. Secondary endpoints included change from baseline in the Clinical Dementia Rating Scale – Sum of Boxes (CDR-SB) and change from baseline of the two components of the iADRS: the Alzheimer's Disease Assessment Scale – Cognitive Subscale (ADAS-Cog 13) and the Alzheimer's Disease Cooperative Study – instrumental Activities of Daily Living subscale (ADCS-iADL) at week 76. There were two primary analysis populations based on visual and quantitative assessment of a tau PET scan: low/medium tau population and combined population of low/medium tau and high tau levels.

The primary efficacy endpoint analysis, change from baseline in iADRS at Week 76, demonstrated a statistically significant treatment effect in the donanemab treatment arm compared to placebo in the combined population (2.92, $p < 0.001$) and the low/medium population (3.25,

p<0.001). Statistically significant reduction in clinical decline in the Division's recommended endpoint, CDR-SB, was also demonstrated, with a treatment effect of -0.70 [-29%], p<0.001 in the combined population. Nominal statistical significance was reached by Week 12 and was maintained through Week 76. Results were robust across sensitivity analyses. Statistically significant results favoring donanemab were observed for the multiplicity-controlled secondary endpoints ADAS-Cog 13 (-1.33 [-20%], p<0.001) and ADCS-iADL (1.70 [-28%], p<0.001), the two endpoints which comprise the iADRS. Donanemab treatment demonstrated a statistically significant treatment effect on change from baseline in brain amyloid as measured by PET and reported as Centiloids at Week 76 (-86.4, p<0.0001).

It is useful to interpret treatment difference as a percent reduction rather than the absolute point difference which depends on the length of the study and the disease stage. The results of Study AACI demonstrate a reduced decline of approximately 20% to 30% on clinical endpoints in the combined population. For CDR-SB, this corresponds to a preservation of CDR-SB by approximately 5.4 months relative to placebo over the 18 months of the study. This preservation of cognitive function is clearly clinically meaningful.

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

Study AACI is a large, multicenter, adequate and well-controlled study that demonstrated statistically persuasive and clinically meaningful benefits in cognition and function in subjects with Alzheimer's disease. The effect on CDR-SB in Study AACI represents a clinically meaningful reduction of clinical decline. This finding is supported by statistically significant results for multiplicity-controlled secondary endpoints, including endpoints capturing distinct information regarding cognitive decline and function. The treatment effect is supported by the consistently favorable results across subgroups of interest defined by demographic and baseline disease characteristics. Biomarkers reflecting brain amyloid plaque load and astrocytic activation support the observations on the clinical endpoints. Study AACG is also an adequate and well-controlled study which provides independent substantiation for the findings in Study AACI and contributes to the evidence of effectiveness.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	- Alzheimer’s disease is a progressive, degenerative brain disorder that affects memory, thinking, and behavior and is the most common cause of dementia. - Clinical symptoms include difficulty remembering recent conversations, names, or events, impaired communication, disorientation, confusion, poor judgment, behavioral changes, and ultimately, difficulty walking, speaking, and swallowing. - Alzheimer’s disease exists on a continuum from biological changes in the brain, to subtle problems with memory and thinking, and ultimately difficulties that affect an individual’s ability to perform everyday activities. The disease process may begin 20 years or more before symptoms arise. - After a diagnosis of Alzheimer’s dementia, the average survival is 4 to 8 years. - An estimated 6.7 million Americans age 65 years and older are currently living with Alzheimer’s disease. - Alzheimer’s disease was the sixth leading cause of death in the United States in 2019. - Almost two-thirds of Americans with Alzheimer’s disease are women. Older African Americans and Latinos are disproportionately more likely to have Alzheimer’s disease than White Americans.	Alzheimer’s disease is a major public health issue that causes substantial impairment in cognition and function and imposes an immense burden on patients and caregivers. The number of Americans with Alzheimer’s disease dementia is expected to increase significantly in the next few decades.
Current Treatment Options	Acetylcholinesterase inhibitors donepezil, rivastigmine, and galantamine, and the N-methyl-D-aspartate receptor antagonist memantine are approved for the treatment of Alzheimer’s disease. These therapies affect the symptoms of the disease but do not change the progressive course of the disease.	There is an urgent and unmet medical need for effective treatments for Alzheimer’s disease. In addition to the general need for more effective treatments, there is a particular unmet need for effective treatments to delay, halt, or

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	- Antipsychotics are commonly prescribed to treat behavioral symptoms but are not approved for the treatment of Alzheimer's disease and are associated with increased mortality in older patients with dementia. - Aducanumab and lecanemab are amyloid beta-directed antibodies that received accelerated approval and traditional approval, respectively, and are indicated for the treatment of Alzheimer's disease, specifically patients with mild cognitive impairment or mild dementia stage of disease.	reverse the pathophysiological processes that ultimately lead to the clinical deficits of Alzheimer's disease.
Benefit	- The efficacy of donanemab in patients at the early stages of symptomatic Alzheimer's disease was evaluated in Study AACI - Participants were randomized 1:1 to receive placebo or donanemab 700 mg administered as an IV infusion every 4 weeks for the first 3 doses, then 1400 mg every 4 weeks for up to 72 weeks. - The trial enrolled 1727 subjects: 853 in the donanemab arm and 874 in the placebo arm. - Two key populations were defined: the overall population, including all enrolled subjects and a low/medium tau population based on tau pathology at baseline. - The primary endpoint was the change from baseline in iADRS at Week 76. iADRS is a simple linear combination of two scores: ADAS-Cog 13 and ADCS-iADL. - Key secondary endpoints were change from baseline to Week 76 in CDR-SB, ADAS-Cog 13, ADCS-iADL, and MMSE. - Key pharmacodynamic endpoints included change from	The results of Study AACI provide persuasive evidence of effectiveness of donanemab. The effect on CDR-SB represents a clinically meaningful reduction of clinical decline. The findings on the primary endpoint are supported by statistically significant results for all clinical endpoints, including endpoints capturing distinct information regarding cognitive decline and function. The treatment effect is supported by the consistently favorable results for the primary and secondary endpoints across subgroups of interest defined by demographic and baseline disease characteristics. Biomarkers reflecting brain amyloid plaque load and astrocytic activation support the observations on the clinical endpoints. Study AACG provides

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	baseline in brain amyloid and tau disposition as measured by PET, brain volumes as measured by volumetric MRI, and plasma levels of neurofilament light chain (NfL), glial fibrillary acidic protein (GFAP), and phosphorylated tau (p-tau 181 and p-tau 217). • Treatment with donanemab demonstrated reduced clinical decline, as evidenced by a statistically significant treatment effect on change from baseline in iADRS compared to placebo in the low/medium tau population (3.25 [-35%], $p < 0.001$) and the overall population (2.92 [-22%], $p < 0.001$) at Week 76. The treatment effect can also be contextualized in terms of time saved, in which the time saved over 76 weeks was 4.4 months in the low/medium tau population and 1.4 months in the overall population. • Donanemab treatment also demonstrated a statistically significant reduction in decline on change from baseline CDR-SB compared to placebo in the low/medium tau population (-0.67 [-36%], $p < 0.001$) and the overall population (-0.70 [-29%], $p < 0.001$) at Week 76. Donanemab treatment resulted in an estimate of time saved over 76 months of 7.5 months in the low/medium tau population and 5.4 months in the overall population. • Statistically significant treatment effects in favor of donanemab were observed for all other multiplicity-controlled secondary clinical endpoints at Week 76 in the low/medium tau population: ADAS-Cog 13 (-1.52 [-32%], $p < 0.001$) and ADCS-iADL (1.83 [-40%], $p < 0.001$) and the overall population: ADAS-Cog 13 (-1.33 [-20%], $p < 0.001$) and ADCS-iADL (1.70 [-28%], $p < 0.001$).	independent substantiation for the findings in Study AACI. Together, the results of these two adequate and well-controlled studies provide substantial evidence of effectiveness for donanemab for the treatment of Alzheimer's disease. There is no information on the need for dosing to maintain clinical benefit after amyloid PET thresholds for dose cessation have been reached. A clinical trial that assesses the safety and efficacy of a maintenance dosing regimen of donanemab is recommended as a post-marketing commitment (PMC).

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• Results were robust to sensitivity analyses. • The donanemab treatment arm had a statistically significant reduction in brain amyloid from baseline to Week 76 compared to the placebo arm (-86.4 Centiloid, $p < 0.0001$). • Treatment effects on phosphorylated tau (p-tau 181 and p-tau 217) and GFAP supported the observations on clinical outcomes. • Favorable results for iADRS and CDR-SB were observed across subgroups of interest. • Study AACG was a smaller study (257 subjects: 131 in the donanemab arm and 126 in the placebo arm) of similar design ○ Donanemab treatment demonstrated a statistically significant reduction in brain amyloid plaque from baseline to Week 76 compared to placebo (-85.1 Centiloid, $p < 0.001$). ○ The primary efficacy endpoint analysis, change from baseline in iADRS at Week 76, demonstrated a statistically significant treatment effect in the donanemab treatment arm compared to placebo (3.20 [-32%], $p = 0.042$). ○ Favorable numerical results for secondary clinical endpoints were observed and were consistent with observations in Study AACI • During an off-treatment period, amyloid PET values began to increase with a median rate of 2.8 Centiloids/year. There is no data beyond the 76-week duration of Study AACI to guide whether additional dosing with donanemab may be needed for longer-term clinical benefit.	

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk and Risk Management	• Please refer to safety review by Dr. Branagan.	

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application

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

2. Therapeutic Context

2.1. Analysis of Condition

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

and behavior and is the most common cause of dementia. According to a recent report (Alzheimer's Association 2024), an estimated 6.9 million Americans age 65 years and older are currently living with Alzheimer's disease dementia. The report noted that Alzheimer's disease is the fifth-leading cause of death for those age 65 years and older. Almost two-thirds of Americans with Alzheimer's disease are women. Older African Americans and Latinos are disproportionately more likely to have Alzheimer's disease than White Americans (Alzheimer's Association 2024).

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

The two pathological hallmarks of Alzheimer's disease are extracellular deposits of A β , or plaques, and intracellular aggregates of hyperphosphorylated tau in the form of neurofibrillary tangles. Accumulation of A β in the brain has been proposed to be the primary driver of the disease process and precedes the accumulation of tau pathology and neural degeneration. Consequently, therapies to inhibit A β production or enhance A β clearance have been investigated in an attempt to slow or halt the disease process. Importantly, "anti-amyloid" therapies are not a distinct class of drugs, but rather reflect many different modes of action. A careful examination of anti-A β therapies has revealed that for therapies targeting aggregated forms of A β there exists a relationship between reduction of brain amyloid plaque and reduction of clinical decline.

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

2.2. Analysis of Current Treatment Options

Treatment goals for patients with Alzheimer's disease are often directed to maintain quality of life, treat cognitive symptoms, and manage behavioral and psychological symptoms of

dementia. Approved Alzheimer's disease treatments include the cholinesterase inhibitors donepezil, rivastigmine, and galantamine, the N-methyl-D-aspartate antagonist memantine, and anti-amyloid beta-directed antibodies. Aducanumab and lecanemab are monoclonal antibodies directed toward aggregated forms of amyloid and are the first therapies to receive accelerated approval and traditional approval, respectively, that target the underlying pathology of the disease.

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

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Donanemab is a new molecular entity (NME) and is not currently marketed in the United States for any indication.

3.2. Summary of Presubmission/Submission Regulatory Activity

IND 109157 for donanemab (previously LY3002813) was opened in the United States on February 5, 2013, for (b) (4) Alzheimer's disease. This summary primarily focuses on regulatory activity related to the BLA submission and resubmission for donanemab. For a summary of regulatory activity prior to the initial BLA submission for accelerated approval refer to the previous clinical efficacy review (Krudys, DARRTS 1/17/2023).

- December 22, 2022 – A Type B meeting was held to discuss the applicant's justification for changing the primary analysis method from a Bayesian disease progression model (DPM) to a natural cubic splines (NCS) model for Study AACI. The Division reminded the applicant that the use of the DPM for the primary efficacy analysis had never been agreed upon with the Division. The Division communicated their concerns with the use of the NCS model and recommended additional simulations to evaluate the type 1 error. In a subsequent submission dated January 3, 2023, the applicant provided additional supporting simulations and calculations. As a post-meeting comment, the Division responded to the January 3, 2023, submission by providing further feedback on the applicant's plan to use the NCS model. The Division also reminded the applicant of the Division's reservations about the use of the iADRS as a primary efficacy measure.
- January 18, 2023 – The Division issued a CR letter because the safety database was

insufficient to adequately characterize the long-term safety of donanemab for the treatment of Alzheimer's disease.

- February 22, 2023 – Written responses were provided in response to a Type B pre-BLA meeting request for feedback on the content and format of a proposed supplemental BLA.
- March 2, 2023 – A Type A meeting was held in response to the CR letter issued by the Division on January 18, 2023. The applicant notified the Division that it intended to seek traditional approval of donanemab under a resubmission to the BLA. The primary outcome of this meeting (and the February 22, 2023, written responses) was an agreement on the adequacy and format of the proposed safety data to address the inadequacies noted in the CR letter.
- June 12, 2023 – Resubmission of BLA 761248.

3.3. Foreign Regulatory Actions and Marketing History

Donanemab is not approved or marketed in any foreign country.

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

4.1. Office of Scientific Investigations (OSI)

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

4.2. Product Quality

The Office of Pharmaceutical Quality (OPQ) review recommends approval and concludes that the data submitted are adequate to support the conclusion that the manufacture of KISUNLA is well-controlled and leads to a product that is pure and potent.

4.3. Clinical Microbiology

Not applicable.

4.4. Nonclinical Pharmacology/Toxicology

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

4.5. Clinical Pharmacology

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

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

The central volume of distribution is measured at 3.36 L. Donanemab undergoes degradation by proteolytic enzymes and is not expected to undergo renal elimination or metabolism by hepatic enzymes. The mean terminal half-life of donanemab is approximately 12.1 days, and its clearance is 0.0255 L/h. Age, sex, or race did not demonstrate a significant impact on the pharmacokinetics of donanemab. Although body weight and maximum ADA titer were found to influence donanemab pharmacokinetics, the resulting changes did not affect clinical efficacy. The review team concludes that no therapeutic individualization is necessary based on intrinsic and extrinsic factors such as age, race, sex, ApoE ϵ 4 genotype, baseline tau levels, renal impairment, hepatic impairment, or ADA status. For additional details, please also refer to the OCP review in DARRTS dated 01/17/2023.

Postbaseline, 793 participants in the donanemab group were evaluable for treatment-emergent ADAs (TE-ADAs) during the treatment period from Study AACI. Of these subjects, TE-ADAs were detected in 693 subjects; these subjects are therefore deemed ADA+ and the ADA incidence is 693/793 (87.4%). Neutralizing antibodies (NAb)s were detected in all the ADA+ subjects (693/693; 100%). The presence of TE-ADAs affected various PK measures, such as $C_{min,ss}$ and AUC_{ss} . Also, the presence of TE-ADAs affected amyloid plaque reduction; subjects with higher maximum ADA titer had less amyloid PET reduction compared to subjects with lower maximum ADA titer. However, the changes in amyloid PET associated with high ADA titer did not translate into changes in efficacy measured on iADRS and CDR-SB up to week 76.

The review team raised concerns about the applicant's proposal to stop treatment after plaque reduction because of limitations including reliance on a 12-month off-treatment period for calculating amyloid PET re-accumulation rate, data from a small subset of subjects for calculating amyloid PET re-accumulation rate beyond 76 weeks, lack of evaluation of long-term

efficacy beyond 76 weeks, and exclusion of participants continuing on donanemab despite meeting dose cessation criteria.

The review noted that ApoE ϵ 4 non-carriers and heterozygotes showed nominally higher treatment benefit and lower ARIA risk compared to homozygotes. Changes in amyloid PET and plasma biomarkers (p-tau217, p-tau181, and GFAP) reflected changes in clinical efficacy. However, given the positive trends in treatment benefit and biomarkers for all subgroups, the review team recommends dosing in all ApoE ϵ 4 genotypes, but describing efficacy and safety data in this subgroup to inform benefit-risk assessment.

4.6. Consumer Study Reviews

Not applicable.

4.7. Devices and Companion Diagnostic Issues

Not applicable.

5. Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

One new clinical study relevant to the evaluation of efficacy was included in the resubmission and is summarized in Table 1. The other study relevant to this review, Study AACG, has also been summarized in the clinical review of the original submission (Krudys, DARTS 1/17/2023).

Clinical Review
Kevin Krudys, PhD
BLA 761248 Resubmission
Kisunla (Donanemab)

Table 1: Tabular Presentation of the Clinical Studies Contributing Efficacy Data Relevant to the Evaluation of Clinical Benefit for this BLA Resubmission

Trial Identity/NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population (per categorization at the time of enrollment)	No. of Centers and Countries
<i>Controlled Studies to Support Efficacy and Safety</i>							
I5T-MC-AACI (Study AACI)/NCT04 437511	Double-blind, placebo-controlled, parallel group	IV infusion over at least 30 minutes <u>Placebo</u> Saline infusion <u>Donanemab</u> 700 mg every four weeks for first 3 doses, followed by 1400 mg every 4 weeks until brain amyloid reaches predefined levels or for a total of 72 weeks	<u>Primary</u> Change from baseline in iADRS at Week 76 <u>Secondary</u> Change from baseline in CDR-SB, ADAS-Cog 13, ADCS-iADL, MMSE, brain amyloid plaque, brain tau, and vMRI measures at Week 76	72-week treatment period 44-week follow-up period	1736	Consistent with a diagnosis of MCI due to Alzheimer's disease or mild Alzheimer's disease dementia based on operationalized criteria from the 2018 NIA-AA Research Framework for Alzheimer's disease MMSE score of 20 to 28 Specific amyloid and tau criteria by PET 60 to 85 years of age	277 centers in 8 countries
I5T-MC-AACG (Study AACG)/NCT0 3367403	Double-blind, placebo-controlled, parallel group	IV infusion over at least 30 minutes <u>Placebo</u> Saline infusion <u>Donanemab</u> 700 mg every four weeks	<u>Primary</u> Change from baseline in iADRS at 18 months <u>Secondary</u> Change from baseline in CDR-SB, ADAS-Cog 13, ADCS-iADL, MMSE,	72-week treatment period 48-week follow-up period	272	Consistent with a diagnosis of MCI due to Alzheimer's disease or mild Alzheimer's disease dementia based on operationalized criteria from the 2018 NIA-AA Research Framework for	56 centers in United States and Canada

Clinical Review
Kevin Krudys, PhD
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Kisunla (Donanemab)

		for first 3 doses, followed by 1400 mg every 4 weeks until brain amyloid reaches predefined levels or for a total of 72 weeks *the original design included a combination therapy arm of donanemab and LY3202626 (BACE1 inhibitor)	brain amyloid plaque, brain tau, and vMRI measures at 18 months			Alzheimer's disease MMSE score of 20 to 28 Positive amyloid load and specific tau criteria by PET 60 to 85 years of age	

5.2. Review Strategy

The purpose of this review is to evaluate whether the results of Study AACG and Study AACI provide substantial evidence of effectiveness to support the traditional approval of donanemab for the treatment of Alzheimer's disease. Study AACG, the relatively smaller Phase 2 study, was reviewed during the original submission for accelerated approval (Krudys, DARRTS 1/17/2023) and will only be briefly summarized in this review. The clinical efficacy review for that submission recommended accelerated approval based on a finding of substantial evidence of effectiveness on a reasonably likely surrogate endpoint. The application received a Complete Response, however, because the safety database was insufficient to adequately characterize the long-term safety of donanemab for the treatment of Alzheimer's disease. In response to the Complete Response letter of January 18, 2023, the applicant submitted the results of the pivotal study, Study AACI. Because accelerated approval was never granted for the original submission, Study AACI is reviewed in the context of providing substantial evidence of effectiveness for traditional approval rather than simply verifying clinical benefit. This review will therefore focus on the results of Study AACI as an adequate and well-controlled large multicenter trial which can provide substantial evidence of effectiveness. The results of Study AACG will be summarized briefly in Section 6 and referenced in the integrated analysis (Section 7.3) as providing additional evidence for efficacy.

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

6. Review of Relevant Individual Trials Used to Support Efficacy

6.1. Study AACI (I5T-MC-AACI) Assessment of Safety, Tolerability, and Efficacy of Donanemab in Early Symptomatic Alzheimer's Disease

6.1.1. Study Design

Overview and Objective

Study AACI was a double-blind, placebo-controlled study to evaluate the safety and efficacy of donanemab in subjects 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 integrated Alzheimer's Disease Rating Scale (iADRS) at 76 weeks.

Trial Design

Study AACI was a multicenter, randomized, double-blind, placebo-controlled, parallel-group

study in subjects with early symptomatic Alzheimer's disease. A total of 277 centers across 8 countries enrolled subjects into the trial. The study included a screening period of up to 7 weeks, a 76-week placebo-controlled treatment period, and an immunogenicity and safety follow-up period of 44 weeks. Subjects were randomized to placebo or donanemab treatment in a 1:1 ratio in the placebo-controlled period.

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

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: $SUVR \leq 1.46$ and a topographic deposition pattern consistent with advanced Alzheimer's disease or $1.10 \leq SUVR \leq 1.46$ and a topographic deposition consistent with moderate Alzheimer's disease
- High tau: $SUVR > 1.46$ and a topographic deposition pattern consistent with either moderate or advanced Alzheimer's disease

Diagnostic Criteria

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 (NIA-AA) Research Framework for Alzheimer's disease (Jack et al. 2018). Subjects were required to have evidence of A β pathology by quantitative assessment on PET and evidence of a topographic tau disposition pattern consistent with Alzheimer's disease. Subjects were also required to have gradual and progressive change in memory function for at least 6 months and evidence of a mild degree of impairment on a screening cognitive assessment.

Key Inclusion Criteria

1. Gradual and progressive change in memory function reported by the patient or informant for ≥ 6 months
2. MMSE score of 20 to ≤ 28
3. Male or female patients age 60 to ≤ 85 years
4. Must have a study partner who is in frequent contact with the patient (at least 10 hours per week)
5. Confirmed presence of amyloid plaques on PET (≥ 37 Centiloids)

6. Confirmed presence of tau on PET
 - a. Topographic deposition consistent with moderate Alzheimer's disease and SUVR ≥ 1.10
 - b. Topographic deposition consistent with advanced Alzheimer's disease

Reviewer Comment: The applicant did not require a formal clinical diagnosis of mild cognitive impairment due to Alzheimer's disease or mild Alzheimer's disease dementia. Instead, subjects were enrolled based on Alzheimer's disease pathology and presence of clinical symptoms and objective evidence of cognitive impairment with scoring in the mild range as assessed by the MMSE. These criteria essentially operationalized the 2018 NIA-AA Research Framework for Alzheimer's disease (Jack et al. 2018) (A+/T+/evidence of cognitive impairment and decline in cognitive performance from baseline). Enrollment criteria for functional status were not specified, but the population would either have no functional impairment or some degree of functional impairment with only a mild range of impairment in cognition which would also be consistent with clinical staging for mild cognitive impairment or mild dementia or Stages 3 and 4 Alzheimer's disease as defined in the FDA Draft Guidance for Early Alzheimer's Disease (February 2018), although it is noted that there is potential for some subjects with a greater degree of functional impairment suggesting a moderate stage of dementia to be enrolled using these criteria.

The specific quantitative criterion for amyloid PET was selected to ensure that subjects would have an adequate amount of amyloid, the pharmacologic target, such that they would be more likely to show a benefit. This specific quantitative criterion was designed to increase the likelihood of observing an effect in the clinical trial and does not need to be replicated in labeling, other than requiring the presence of amyloid beta pathology. Likewise, the tau PET criteria were chosen to enrich the population such that subjects would be more likely to experience clinical progression during the study and do not need to be replicated in labeling. Further discussion of efficacy across the spectrum of tau is provided in Section 7.1.3.

Key Exclusion Criteria

1. Significant neurological disease affecting the central nervous system, other than Alzheimer's disease, that may affect cognition or ability to complete the study
2. Current serious or unstable illnesses including cardiovascular, hepatic, renal, gastroenterologic, respiratory, endocrinologic, psychiatric, immunologic, or hematologic diseases that could interfere with study procedures
3. History of clinically significant multiple or severe drug allergies, significant atopy, or severe posttreatment hypersensitivity reactions
4. Screening MRI showing evidence of a significant abnormality that would suggest another potential etiology for progressive dementia

5. MRI demonstrating presence of ARIA-E, >4 cerebral microhemorrhages, more than 1 area of superficial siderosis, any macrohemorrhage, or severe white matter disease at screening
6. Alanine aminotransaminase (ALT) $\geq 2.5X$ the upper limit of normal (ULN), aspartate aminotransferase (AST) $\geq 2.5X$ ULN, total bilirubin level (TBL) $\geq 1.5X$ ULN, or alkaline phosphatase (ALP) ≥ 2 ULN at screening
7. Prior treatment with a passive anti-amyloid immunotherapy <5 half-lives prior to randomization or active immunization against A β in any other study

Dose Selection

The dosing regimen was based on safety, PK, and PD results from earlier dose-ranging studies and was chosen to balance amyloid plaque reduction and occurrence of ARIA. Briefly, doses lower than 10 mg/kg (equivalent to 700 mg in a 70 kg individual) were not associated with robust amyloid plaque reduction and a single dose of 40 mg/kg (equivalent to 2800 mg in a 70 kg individual) was associated with an unacceptable risk of ARIA. Therefore, a dose of 1400 mg was chosen as the target dose. 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 3 doses.

The protocol mandated dose cessation based on meeting specific brain amyloid thresholds. The applicant argues that amyloid plaque is the only amyloid species engaged by donanemab and therefore there is no reason to continue dosing once amyloid plaque has been reduced below a certain level.

Reviewer Comment: The decision to cease dosing once amyloid plaque is reduced below a certain threshold is not unreasonable, but there is remaining uncertainty regarding the applicant's approach as there is no direct comparison to a group of subjects who had similar plaque reduction but continued dosing. Also, the threshold commonly used to denote amyloid negativity is a useful measure, but it is still possible there could be added benefit to reducing amyloid further in this patient population. Importantly, the duration of follow-up is insufficient to assess long-term consequences of dose cessation. Therefore, there remains uncertainty regarding the optimal dosing regimen for amyloid-targeting monoclonal antibodies once amyloid plaque has been reduced to a very low level.

Study Treatments

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

Assignment to Treatment

An interactive web response system (IWRS) was used to assign subjects to treatment groups. Subjects were randomized equally to placebo or donanemab. Randomization was stratified by investigative site and tau pathology (low/medium or high).

Blinding

Study drug was dispensed by an unblinded pharmacist or other qualified personnel at each site. All other study site staff and subjects were blinded to treatment assignment. Investigators, subjects, and study partners were not informed of results of PET scans during the double-blind portion of the trial. The protocol specified that that CDR rater should also be blinded to adverse events (AEs).

Dose Modification/Dose Discontinuation

Double-blind dose cessation of donanemab was guided by amyloid PET levels measured at Week 24, Week 52, and Week 76. Subjects 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 2 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 subjects who developed ARIA and had dose suspension during titration, the investigator could elect to reinitiate and continue dosing with 700 mg or continue with the planned titration to 1400 mg.

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

Safety Addendum

A safety addendum was added to Study AACI to collect open-label safety data in up to approximately 1000 subjects with early symptomatic Alzheimer's disease who had evidence of amyloid pathology. Subjects were to receive open-label donanemab at the dosing regimen described earlier. The inclusion and exclusion criteria were similar to those for the placebo-

controlled period, except the tau PET criterion was removed. Subjects who did not meet the criteria for participation in the main study were allowed to screen for the addendum if screen failure was due to a non-eligible tau PET scan or non-eligible amyloid PET scan if the amyloid level was between 24.3 and 37.1 Centiloids. Clinical efficacy assessments were not collected in the safety addendum. Change in brain amyloid plaque deposition and blood-based biomarkers were included as endpoints.

Administrative Structure

An independent Data Monitoring Committee (DMC) was formed to monitor the study and review safety on an ongoing basis. The DMC was to consist of at least 3 members, including a physician with expertise in Alzheimer's disease and a statistician. A statistical analysis center (SAC), consisting of third-party statisticians, prepared unblinded data for the DMC.

Procedures and Schedule

The schedule of key assessments is provided in Table 2. The lead-in screening period occurred any time prior to the screening visit and was used to collect demographic data and administer the MMSE. A period of 49 days was allowed for completion of the screening visit assessments. Study visits occurred every 4 weeks for 76 weeks with follow-up visits beginning 12 weeks after the last dose.

Table 2: Study AACI Schedule of Key Assessments

Assessment	Schedule
Eligibility Criteria	Screening, Week 0
ApoE Genotyping	Lead-In
Neurological and Physical Examinations	Screening, Weeks 0, 12, 24, 36, 52, 64, 76, Early Discontinuation
MRI	Screening, Weeks 4, 12, 24, 52, 76, Early Discontinuation
Study Drug Administration	Weeks 0, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, 56, 60, 64, 68, 72
Anti-Donanemab Ab	Weeks 0, 4, 8, 12, 16, 24, 36, 52, 76, Early Discontinuation, Follow-up
Donanemab Concentration	Weeks 0, 4, 8, 12, 16, 24, 36, 52, 64, 76, Early Discontinuation, Follow-up
Blood for Biomarker Analysis	Lead-In, Weeks 0, 12, 24, 36, 52, 64, 76, Early Discontinuation
Amyloid PET	Screening, Weeks 24, 52, 76, Early Discontinuation
Tau PET	Screening, Week 76, Early Discontinuation
MMSE	Lead-In, Weeks 0, 12, 24, 36, 52, 64, 76, Early Discontinuation
CDR-SB, ADAS-Cog13, ADCS-ADL, DSST	Weeks 0, 12, 24, 36, 52, 64, 76, Early Discontinuation

Created by the reviewer, modified from Schedule of Activities table in protocol

Abbreviations: Ab, antibody; ADAS-Cog, Alzheimer's Disease Assessment Scale – Cognitive Subscale; ADCS-ADL, Alzheimer's Disease Cooperative Study – Activities of Daily Living; CDR-SB, Clinical Dementia Rating – Sum of Boxes; DSST, Digit Symbol Substitution Test; MMSE, Mini-Mental State Examination; MRI, Magnetic Resonance Imaging.

Concurrent Medications

Treatment of Alzheimer's disease with cholinesterase inhibitors and/or memantine was allowed if the dose had been unchanged for approximately 30 days before randomization. During the study, subjects could initiate these medications or modify their doses if deemed medically necessary. Immunoglobulin therapy was not allowed during the study.

Treatment Compliance

Subjects who attended the study visit and successfully received a complete donanemab or placebo infusion were considered to be compliant. A complete infusion is one in which at least 75% of the infusion solution was given.

Subject Completion, Discontinuation, or Withdrawal

Completers were defined as subjects who completed all required phases of the study, including the last visit or the last scheduled procedure.

Subjects permanently discontinued from study treatment were to remain in the study. Subjects who prematurely discontinued from the study were to return for an early discontinuation visit and follow-up visits with clinical assessments as outlined in Table 2. Reasons for discontinuation include AE, death, lost to follow-up, physician decision, progressive disease, withdrawal by subject, and withdrawal due to caregiver circumstances.

Study Endpoints

Primary Efficacy Endpoint

The primary endpoint was the change from baseline in integrated Alzheimer's Disease Rating Scale (iADRS) at Week 76. The iADRS is a simple 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).

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

Secondary Clinical Endpoints

CDR-SB

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

Reviewer Comment: At the March 2, 2021, Type C Meeting the Division included the following statement in a post-meeting note, "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."

ADAS-Cog 13

The ADAS-Cog is a cognitive assessment consisting of clinical ratings and cognitive tasks that was originally developed for use in clinical trials of patients with later stages of Alzheimer's disease dementia. ADAS-Cog 11 includes 11 tasks measuring disturbances of memory, language, and praxis. Many of the items of the ADAS-Cog 11 are at the measurement floor in patients with mild disease and may not show decline over the length of a typical clinical trial. Therefore, two additional tasks, delayed word recall and number cancellation, were added to create the ADAS-Cog 13 for use in this earlier disease population. The ADAS-Cog 13 includes 9 items that test performance (up to 65 points) and 4 clinician-rated items that test language and memory (up to 20 points) for a total score ranging from 0 to 85, with higher scores indicating greater cognitive impairment. The 13 items assess word recall, ability to follow commands, constructional praxis, naming, ideation praxis, orientation, word recognition, comprehension of spoken language, memory, word-finding, language ability, delayed word recall, and concentration.

ADCS-iADL

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

MMSE

The MMSE is a widely used performance-based assessment of cognitive ability consisting of 11 tasks evaluating orientation, word recall, attention and calculation, language, and visuospatial functions. The scores from the 11 tests are summed to obtain a total score, which ranges from 0 to 30, with lower scores indicating greater cognitive impairment. It is often used as a screening assessment in clinical practice or as a staging instrument for trial inclusion and is also used as an efficacy assessment in clinical trials.

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

Cognitive and functional assessments were conducted with an electronic Clinical Outcome Assessment (eCOA) tablet. Testing for each subject was to be performed at approximately the same time of day on each visit. The CDR-SB and the ADCS-ADL were to be administered by the same rater. The ADAS-Cog 13 and MMSE were to be administered by a separate rater. Whenever possible, these 2 raters were to administer the same assessments to the same individual subject throughout the study.

Biomarker Endpoints

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

Exploratory Endpoints

DSST

The digit symbol substitution test (DSST) is a computer-administered neuropsychological test. Images of different types of medicines are presented as symbols and numeric calendar dates are numbers. Patients are shown a legend that indicates associations between 9 medicines and 9 calendar dates. The patient is instructed to consider each empty box in relation to the date-medicine association in the legend and select the medicine associated with the empty date box

from a group of images. The performance measure is the number of correct associations between date and medicine made within 120 seconds.

Time to Substantial Decline

Time to a clinical worsening event was defined as meeting the following criteria at 2 consecutive visits:

- Any increase in CDR global score
- ≥ 1 point increase in CDR-SB for subjects with MMSE at screening of 27-30 or a ≥ 2 points increase for subjects with MMSE at screening of 20-26
- 5 points decrease in iADRS for subjects with MMSE at screening of 27-30 or 9 points decrease for subjects with MMSE at screening of 20-26

Responder Analyses

The probability of not progressing, defined as having a CDR-SB change from baseline ≤ 0 , was calculated at each scheduled visit. Additional exploratory analyses were performed for iADRS and CDR-SB to determine whether subjects met a prespecified percentage of disease slowing at month 12 and month 18 based on the estimated placebo decline.

Statistical Analysis Plan

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

Definitions of Statistical Analysis Populations

The following analysis populations were the key populations defined in the SAP:

- Randomized – all subjects who signed the informed consent form and were randomized to study treatment
- Evaluable Efficacy – all randomized subjects with a baseline and at least one post-baseline efficacy scale
- Per-Protocol – all subjects in the Evaluable Efficacy dataset who also signed the informed consent form, had an assessment of the primary endpoint at each scheduled visit completed, had no violations of inclusion/exclusion criteria, had no instances of receiving the wrong treatment, and were not considered non-compliant with regard to

study drug

Two additional populations are critical for interpretation of the study results: the low/medium tau population and the overall population. The low/medium tau population is defined by tau PET SUV and visual read as described earlier in the review. The overall population is the combination of the low/medium tau population and the high tau population.

Reviewer Comment: This review will present the results for both the low/medium and overall populations because they were prespecified in the statistical analysis plan. For assessment of effectiveness, however, this review will focus on the overall population, as this is the relevant population with respect to the proposed indication. It is also worth noting that these two populations are not independent, as the low/medium population makes up 68% of the overall population.

Sample Size Determination

Sample size calculations were based on the low/medium tau population. Based on the results of Study AACG, the sample size calculation assumed a standard deviation of change from baseline in iADRS at 18 months of 11.06, a treatment difference of 3.2, and a discontinuation rate of 30%. Of the approximately 1800 subjects enrolled in the study it was assumed that approximately two-thirds of the population would have low/medium tau levels. Under these assumptions, the sample size provided greater than 95% power to achieve statistical significance at a 1-sided 0.025 level.

Interim Analyses

Interim analyses for efficacy were not performed.

Analysis Method for Primary Endpoint

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

Additional Analysis Methods

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

A time progression model for repeated measures (PMRM) was used to estimate the slowing of progression of the disease, in terms of time, for the donanemab treatment group compared to the placebo group (Raket, 2022). A natural cubic spline model with internal knots at each planned visit was used to interpolate the disease progression for the placebo arm. The donanemab disease progression was described by assuming that it could be estimated by the mean disease progression of the placebo group at another time point. The assumption of proportional time slowing was tested.

A Cox proportional hazard model was used for the time to substantial decline analyses. The analyses were modeled as time to first occurrence of the event adjusting for baseline age, score, and use of AD medication at baseline and stratified by pooled investigator sites.

A generalized linear mixed model (GLMM) with progression status (yes or no) as the dependent variable with a binary distribution was used to assess the difference in probability of not progressing by treatment arm. The model included baseline score, baseline score-by-visit interaction, treatment, visit, treatment-by-visit interaction, use of AD medication at baseline, and age at baseline as fixed effects.

Adjustments for Multiplicity

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

Subgroup Analyses

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

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

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- Sex (male, female)
- Race (White, Black or African American, Asian)
- Ethnicity (Hispanic or Latino, not Hispanic or Latino)
- ApoE ε4 carrier status (carrier, non-carrier)
- ApoE ε4 genotype (non-carrier, heterozygous carrier, homozygous carrier)
- Clinical staging at screening (MMSE 20-26, MMSE 27-28)
- Baseline brain tau category (low/medium, high)
- Baseline tau SUVR tercile defined by screening MUBADA SUVR
- BMI (<25, 25-30, ≥30 kg/m²)

The NCS2 model was to be used to perform subgroup analyses for iADRS, CDR-SB, ADAS-Cog 13, ADCS-iADL, and MMSE. MMRM models were used to perform analyses for amyloid PET and plasma biomarker endpoints. An ANCOVA analysis was used for the tau PET endpoints.

Protocol Amendments

The original protocol was issued on January 30, 2020, and was amended 5 times (versions (a) through (e)). Protocol amendment (a) changed the dosing regimen to include titration with 700 mg for the first 3 doses due to a higher-than-expected incidence of serious ARIA-E in the first 43 treated subjects. Protocol amendment (b) in February 2021 increased the sample size and converted the study from a Phase 2 study to a Phase 3 study to confirm the results observed in Study AACG. The primary endpoint was changed from CDR-SB in the overall or low/medium tau population to iADRS in the low/medium tau population. In version (d) a long-term extension was added to the study and the CDR was allowed to be administered to the participant or study partner by telephone. The primary analysis method was changed from Bayesian Disease Progression Model to NCS in version (e) in November 2022.

6.1.2. Study Results

Compliance with Good Clinical Practices

The applicant attests that the study was conducted in accordance with the principles of GCP and applicable laws and regulations.

Financial Disclosure

The applicant has adequately disclosed financial interests or agreements with clinical investigators as outlined in the guidance for industry Financial Disclosures by Clinical Investigators. There were 4 investigators at 4 different sites with disclosable financial interests or arrangements, but those sites do not have the potential to influence the overall results because of the low numbers of subjects they enrolled.

Patient Disposition

A total of 8240 subjects were screened for entry into the study and 1736 were randomized. The most common reasons for screen failure were failure to meet inclusion criteria for amyloid PET (25%), tau PET (25%) or MMSE (23%). Patient disposition is summarized in Table 3. There were 9 subjects who were randomized (2 placebo, 7 donanemab) but discontinued before receiving study treatment. A total of 137 subjects (52 placebo, 85 donanemab) were not included in the evaluable efficacy population for the primary endpoint because they did not have a baseline assessment and/or at least one post-baseline iADRS assessment or were discontinued before receiving study treatment. There were 50 subject (20 placebo, 30 donanemab) missing a baseline iADRS assessment.

Reviewer Comment: The percentage of subjects with missing baseline measurements for the primary outcome assessment (3%) was relatively higher than that observed in other recent studies. It is noteworthy that the number of missing baseline measurements for CDR-SB was less than half that for iADRS, which requires two separate assessments (ADAS-Cog 13 and ADCS-ADL). Subjects with missing baseline assessments are automatically excluded from the evaluable efficacy population and represent an unfortunate loss of valuable follow-up data, especially considering that most subjects with missing baseline iADRS went on to complete the study.

There was an imbalance in the proportion of subjects discontinuing due to AEs (2.4% placebo, 5.8% donanemab) as well as a larger number of subjects in the donanemab arm who chose to withdraw from the study. There were also 12 subjects (7 donanemab, 5 placebo) who did not complete a final visit prior to data lock.

Although administration of the CDR by telephone was allowed, 98% of assessments were administered in-person at study visits, with only 13 (7 placebo, 6 donanemab) CDR assessments performed remotely at the Week 76 visit.

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

Table 3: Study AACI Patient Disposition

Disposition	Study AACI	
No. of patients screened	8240	
No. of patients not randomized	6504	
	Donanemab N=860 n (%)	Placebo N=876 n (%)
Patients randomized	860	876
Evaluable Efficacy (iADRS)	775 (90%)	824 (94%)
Evaluable Efficacy (CDR-SB)	794 (92%)	838 (96%)
Evaluable Efficacy (ADAS-Cog 13)	797 (93%)	841 (96%)
Evaluable Efficacy (ADCS-iADL)	780 (91%)	826 (94%)
Discontinued treatment	252 (29%)	176 (20%)
Adverse event	98 (11%)	28 (3%)
Consent withdrawn	90 (11%)	93 (11%)
Death	14 (2%)	9 (1%)
Caregiver circumstance	16 (2%)	18 (2%)
Physician decision	18 (2%)	10 (1%)
Progressive disease	4 (<1%)	7 (<1%)
Lost to follow-up	9 (1%)	10 (1%)
Discontinued study	231 (27%)	173 (20%)
Adverse event	50 (6%)	21 (2%)
Consent withdrawn	111 (13%)	94 (11%)
Death	15 (2%)	10 (1%)
Caregiver circumstance	21 (2%)	20 (2%)
Physician decision	19 (2%)	10 (1%)
Progressive disease	4 (<1%)	7 (<1%)
Lost to follow-up	11 (1%)	11 (1%)

Created by reviewer using Table AACI.8.2 in Study AACI CSR

Protocol Violations/Deviations

Protocol deviations that had the potential to affect subject safety or efficacy endpoints were observed in 1242 (71.6%) subjects in the study (621 in the donanemab treatment arm and 622 in the placebo arm). The most common category of deviations was related to study procedure compliance (51% in the donanemab treatment arm and 48% in the placebo arm). Review of these deviations did not reveal systemic issues which would affect the interpretation of the study results. Other important protocol deviations were generally balanced between the two arms.

There were 7 instances of investigational product unblinding occurring in 7 subjects (4 in the donanemab treatment arm and 3 in the placebo arm) at 5 different clinical sites. Detailed narratives describing the unblinding events did not reveal systemic issues and corrective and preventive actions were taken in response to the events.

Table of Demographic Characteristics

Table 4 contains important information regarding demographic characteristics for each arm in the randomized population. The low/medium tau and the overall populations are highlighted because they are the two key populations for the prespecified analysis plan. Demographic characteristics were balanced across the treatment arms and generally representative of the patient population except for an under-representation of African American and Hispanic patients. Overall, 72% of subjects were enrolled in the United States. Demographic characteristics were largely similar in the low/medium tau and overall populations.

Table 4: Study AACI Baseline Demographics (Randomized Population)

	Low/Medium Tau Population			Overall Population		
	Placebo N=594 n(%)	Donanemab N=588 n(%)	Total N=1182 n(%)	Placebo N=876 n(%)	Donanemab N=860 n(%)	Total N=1736 n(%)
Sex						
Male	273 (46.0%)	263 (44.7%)	536 (45.3%)	373 (42.6%)	367 (42.7%)	740 (42.6%)
Female	321 (54.0%)	325 (55.3%)	646 (54.7%)	503 (57.4%)	493 (57.3%)	996 (57.4%)
Age						
Mean (SD)	74.3 (5.8)	74.3 (5.7)	74.3 (5.7)	73.0 (6.2)	73.0 (6.2)	73.0 (6.2)
Median	75.0	74.0	75.0	73.5	73.0	73.0
(Min, Max)	(59.0, 85.0)	(59.0, 86.0)	(59.0, 86.0)	(59.0, 85.0)	(59.0, 86.0)	(59.0, 86.0)
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%)

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Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Table 5 contains a summary of key baseline disease characteristics and baseline use of concomitant Alzheimer's disease medications (i.e., cholinesterase inhibitors or memantine) for both the low/medium tau and overall populations. Disease characteristics are balanced across treatment arms and reflect a population early in the course of Alzheimer's disease. The percentage of the overall population who were ApoE ε4 carriers (70%) is consistent with other studies in this population as is the proportion of subjects receiving concomitant medications for Alzheimer's disease (61%). A clinical diagnosis of MCI due to Alzheimer's disease or mild Alzheimer's dementia was not required for study entry and some subjects were apparently enrolled prior to diagnosis. Baseline characteristics are consistent with an operationalization of the 2018 NIA-AA Research Framework for Alzheimer's disease (A+/T+/evidence of cognitive impairment and decline in cognitive performance from baseline). Overall, the mean baseline scores on the CDR-SB, MMSE, ADAS-Cog 13, and the ADCS-iADL appear to be consistent with a population with mild cognitive impairment and mild to minimal impairment, although there are a few outliers who had more marked impairment on these assessments. It is notable that there were 487 subjects (28%) whose MMSE score at the baseline visit was no longer within the range used for inclusion at screening (415 subjects with MMSE <20 and 72 subjects with MMSE >28 as baseline). This observation was generally balanced in proportion between the two arms and is unlikely to significantly alter the interpretation of the results.

Table 5: Study AACI Baseline Disease Characteristics (Randomized Population)

	Low/Medium Tau Population			Overall Population*		
	Placebo N=594 n(%)	Donanemab N=588 n(%)	Total N=1182 n(%)	Placebo N=876 n(%)	Donanemab N=860 n(%)	Total N=1736 n(%)
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%)
Non-Carrier	164 (27.6%)	166 (28.2%)	330 (27.9%)	251 (28.7%)	259 (30.1%)	510 (29.4%)
Missing	3 (0.5%)	1 (0.2%)	4 (0.3%)	4 (0.5%)	3 (0.3%)	7 (0.4%)
Number of Years Since Diagnosis of AD						
Mean (SD)	1.4 (1.8)	1.5 (1.8)	1.4 (1.8)	1.4 (1.8)	1.5 (1.8)	1.5 (1.8)
Median	0.7	0.8	0.7	0.7	0.8	0.8
Min, Max	(-1.5, 15.5)	(-0.5, 13.5)	(-1.5, 15.5)	(-1.5, 15.5)	(-0.5, 13.5)	(-1.5, 15.5)
Missing	5.0 (0.8%)	7.0 (1.2%)	12.0 (1.0%)	7.0 (0.8%)	8.0 (0.9%)	15.0 (0.9%)
Concomitant AD Medication						
Y	341 (57.4%)	332 (56.5%)	673 (56.9%)	538 (61.4%)	521 (60.6%)	1059 (61.0%)
N	253 (42.6%)	256 (43.5%)	509 (43.1%)	338 (38.6%)	339 (39.4%)	677 (39.0%)
Baseline CDR-SB						
Mean (SD)	3.7 (2.0)	3.7 (2.1)	3.7 (2.1)	3.9 (2.1)	4.0 (2.1)	3.9 (2.1)

	Low/Medium Tau Population			Overall Population*		
	Placebo N=594 n(%)	Donanemab N=588 n(%)	Total N=1182 n(%)	Placebo N=876 n(%)	Donanemab N=860 n(%)	Total N=1736 n(%)
Median	3.5	3.5	3.5	3.5	3.5	3.5
Min, Max	(0.0, 15.0)	(0.0, 11.0)	(0.0, 15.0)	(0.0, 15.0)	(0.0, 11.0)	(0.0, 15.0)
Missing	3.0 (0.5%)	8.0 (1.4%)	11.0 (0.9%)	7.0 (0.8%)	15.0 (1.7%)	22.0 (1.3%)
Baseline CDR global score						
0.5	387 (65.2%)	382 (65.0%)	769 (65.1%)	532 (60.7%)	514 (59.8%)	1046 (60.3%)
1	185 (31.1%)	177 (30.1%)	362 (30.6%)	308 (35.2%)	304 (35.3%)	612 (35.3%)
2	16 (2.7%)	19 (3.2%)	35 (3.0%)	25 (2.9%)	25 (2.9%)	50 (2.9%)
0	3 (0.5%)	2 (0.3%)	5 (0.4%)	4 (0.5%)	2 (0.2%)	6 (0.3%)
Missing	3 (0.5%)	8 (1.4%)	11 (0.9%)	7 (0.8%)	15 (1.7%)	22 (1.3%)
Baseline MMSE						
Mean (SD)	22.8 (3.8)	23.0 (3.6)	22.9 (3.7)	22.2 (3.9)	22.4 (3.8)	22.3 (3.9)
Median	23.0	23.0	23.0	22.0	23.0	22.0
Min, Max	(6.0, 30.0)	(12.0, 30.0)	(6.0, 30.0)	(6.0, 30.0)	(11.0, 30.0)	(6.0, 30.0)
Missing	0	5.0 (0.9%)	5.0 (0.4%)	5.0 (0.6%)	10.0 (1.2%)	15.0 (0.9%)
Screening MMSE						
≥27	116 (19.6%)	115 (19.6%)	231 (19.6%)	137 (15.7%)	146 (17.0%)	283 (16.3%)
20-26	477 (80.4%)	472 (80.3%)	949 (80.4%)	738 (84.3%)	713 (82.9%)	1451 (83.6%)
<20	0 (0%)	1 (0.2%)	1 (0.1%)	0 (0%)	1 (0.1%)	1 (0.1%)
Missing	1	0	1	1	0	1
Baseline ADAS-cog 13						
Mean (SD)	27.8 (8.4)	27.5 (8.4)	27.6 (8.4)	29.3 (8.9)	28.7 (8.8)	29.0 (8.9)
Median	28.0	28.0	28.0	29.0	28.0	29.0
Min, Max	(4.0, 69.0)	(6.0, 64.0)	(4.0, 69.0)	(4.0, 69.0)	(6.0, 64.0)	(4.0, 69.0)
Missing	3.0 (0.5%)	3.0 (0.5%)	6.0 (0.5%)	6.0 (0.7%)	7.0 (0.8%)	13.0 (0.7%)
Baseline ADCS iADL						
Mean (SD)	48.3 (7.9)	48.1 (7.9)	48.2 (7.9)	47.8 (7.8)	47.8 (7.9)	47.8 (7.9)
Median	50.0	50.0	50.0	49.0	49.0	49.0
Min, Max	(13.0, 59.0)	(14.0, 59.0)	(13.0, 59.0)	(13.0, 59.0)	(6.0, 59.0)	(6.0, 59.0)
Missing	9.0 (1.5%)	18.0 (3.1%)	27.0 (2.3%)	18.0 (2.1%)	27.0 (3.1%)	45.0 (2.6%)
Baseline iADRS						
Mean (SD)	105.5 (13.7)	105.7 (13.8)	105.6 (13.8)	103.6 (14.0)	104.1 (14.3)	103.8 (14.2)
Median	107.0	108.0	107.0	105.0	106.0	105.0
Min, Max	(47.0, 139.0)	(42.0, 135.0)	(42.0, 139.0)	(47.0, 139.0)	(31.0, 135.0)	(31.0, 139.0)
Missing	11.0 (1.9%)	19.0 (3.2%)	30.0 (2.5%)	20.0 (2.3%)	30.0 (3.5%)	50.0 (2.9%)
Baseline Amyloid PET (Centiloid)						
Mean (SD)	100.9 (35.1)	102.4 (34.7)	101.6 (34.9)	101.6 (34.5)	103.5 (34.5)	102.5 (34.5)
Median	99.6	101.3	100.4	100.4	101.9	101.5
Min, Max	(36.9, 262.8)	(33.5, 234.1)	(33.5, 262.8)	(36.9, 262.8)	(33.5, 234.1)	(33.5, 262.8)
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	1.2	1.2	1.2	1.3	1.3	1.3
Min, Max	(0.8, 1.5)	(0.9, 1.5)	(0.8, 1.5)	(0.8, 2.5)	(0.9, 2.2)	(0.8, 2.5)
Missing	0	0	0	58 (6.6%)	44 (5.1%)	102 (5.9%)

* 2 subjects in the overall population are missing baseline tau assessment

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Selected baseline disease characteristics for the high tau population are provided in Table 6 to allow direct comparison to the low/medium tau population. Although there is significant overlap, subjects with high tau burden tend to exhibit greater impairment on baseline cognitive assessments compared to subjects with low/medium tau burden.

Table 6: Study AACI Baseline Disease Characteristics (High Tau Population)

	High Tau Population		
	Placebo N=281 n(%)	Donanemab N=271 n(%)	Total N=552 n(%)
Laboratory ApoE4 status			
Carrier	193 (68.7%)	176 (64.9%)	369 (66.8%)
Heterozygote	147 (52.3%)	123 (45.4%)	270 (48.9%)
Homozygote	46 (16.4%)	53 (19.6%)	99 (17.9%)
Non-Carrier	87 (31.0%)	93 (34.3%)	180 (32.6%)
Missing	1 (0.4%)	2 (0.7%)	3 (0.5%)
Number of Years Since Diagnosis of AD			
Mean (SD)	1.6 (1.8)	1.5 (1.7)	1.5 (1.7)
Median	0.9	0.8	0.8
Min, Max	(-0.3, 11.5)	(-0.4, 8.0)	(-0.4, 11.5)
Missing	2.0 (0.7%)	1.0 (0.4%)	3.0 (0.5%)
Concomitant AD Medication			
Y	197 (70.1%)	188 (69.4%)	385 (69.7%)
N	84 (29.9%)	83 (30.6%)	167 (30.3%)
Baseline CDR-SB			
Mean (SD)	4.4 (2.0)	4.4 (2.0)	4.4 (2.0)
Median	4.0	4.5	4.0
Min, Max	(0.0, 13.0)	(1.0, 11.0)	(0.0, 13.0)
Missing	4.0 (1.4%)	7.0 (2.6%)	11.0 (2.0%)
Baseline CDR global score			
0.5	144 (51.2%)	132 (48.7%)	276 (50.0%)
1	123 (43.8%)	126 (46.5%)	249 (45.1%)
2	9 (3.2%)	6 (2.2%)	15 (2.7%)
0	1 (0.4%)	0	1 (0.2%)
Missing	4 (1.4%)	7 (2.6%)	11 (2.0%)
Baseline MMSE			
Mean (SD)	20.8 (3.9)	21.1 (3.9)	20.9 (3.9)
Median	21.0	21.0	21.0
Min, Max	(8.0, 30.0)	(11.0, 30.0)	(8.0, 30.0)
Missing	5.0 (1.8%)	5.0 (1.8%)	10.0 (1.8%)
Screening MMSE			
≥27	21 (7.5%)	31 (11.4%)	52 (9.4%)
20-26	260 (92.5%)	240 (88.6%)	500 (90.6%)
<20	0 (0%)	0 (0%)	0 (0%)
Missing	0	0	0
Baseline iADRS			
Mean (SD)	99.4 (13.8)	100.6 (14.7)	100.0 (14.2)
Median	101.0	102.0	102.0
Min, Max	(58.0, 133.0)	(31.0, 129.0)	(31.0, 133.0)
Missing	9.0 (3.2%)	11.0 (4.1%)	20.0 (3.6%)
Baseline Amyloid PET			
Mean (SD)	103.1 (33.1)	106.0 (33.8)	104.5 (33.5)

	High Tau Population		
	Placebo N=281 n(%)	Donanemab N=271 n(%)	Total N=552 n(%)
Median	102.9	103.5	103.1
Min, Max	(38.7, 213.3)	(38.6, 203.8)	(38.6, 213.3)

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Selected baseline disease characteristics for the no or very low tau population enrolled in the Study AACI Safety Addendum are provided in Table 7. Baseline characteristics overlap with the overall population enrolled in Study AACI, but subjects tended to be earlier in their disease progression, as demonstrated by lower baseline amyloid, higher screening MMSE, and less use of concomitant medication for Alzheimer's disease.

Table 7: Study AACI Safety Addendum Baseline Characteristics (No/Very Low Tau Population)

	Donanemab N=250 n(%)
Laboratory ApoE4 status	
Carrier	148 (59.2%)
Heterozygote	127 (50.8%)
Homozygote	21 (8.4%)
Non-Carrier	101 (40.4%)
Missing	1 (0.4%)
Number of Years Since Diagnosis of AD	
Mean (SD)	1.3 (2.0)
Median	0.4
Min, Max	(-0.1, 16.7)
Missing	0
Concomitant AD Medication	
Y	86 (34.4%)
N	164 (65.6%)
Age	
Mean (SD)	75.1 (5.8)
Median	76.0
(Min, Max)	(60.0, 86.0)
Sex	
Male	125 (50.0%)
Female	125 (50.0%)
Screening MMSE	
≥27	99 (39.6%)
20-26	151 (60.4%)
<20	0 (0%)
Missing	0
Baseline Amyloid PET	
Mean (SD)	76.1 (31.0)
Median	71.7
Min, Max	(25.7, 178.1)

Source: Table APP.7 and adept.xpt and adsl.xpt in 11/21/2023 regulatory response

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Compliance to treatment was based on the number of subjects receiving an infusion at a given visit. Compliance ranged from 98.2% to 100% in the donanemab treatment arm and from 99.7% to 100% in the placebo arm depending on the visit. Although compliance was high, dose modifications due to adverse events, including ARIA, meant that some subjects received fewer than the 19 planned doses. For example, the mean number of infusions in the donanemab treatment arm was 14.6, compared with 16.3 in the placebo arm. A total of 42.2% of subjects in the donanemab treatment arm and 54.9% in the placebo arm received ≥ 19 doses.

In the donanemab treatment arm, the dose could have been reduced to 0 mg based on amyloid PET results at Weeks 24, 52, and 76 as described earlier. Of the subjects in the donanemab treatment arm who had dosing records at Week 28 (the first donanemab administration after the Week 24 PET results), 16% were receiving 0 mg. By Weeks 56 and 78, the percentage of subjects in the donanemab treatment arm with dosing records receiving 0 mg was 46% and 69%, respectively. At Week 78 (the first dosing period in the long-term extension), a total of 29% of subjects randomized to the donanemab arm were still receiving 1400 mg.

Overall, 10% of study participants started a new concomitant Alzheimer's disease medication at some point during the study (12% in the placebo arm and 8% in the donanemab arm) and 4.4% (5.7% in the placebo arm and 3.2% in the donanemab arm) changed the dose of an existing Alzheimer's disease medication. The relatively higher proportion of subjects in the placebo arm starting a new concomitant medication could potentially make it more difficult to demonstrate a treatment effect in the study.

Efficacy Results – Primary Endpoint

The donanemab treatment arm demonstrated a statistically significant treatment effect on the primary efficacy endpoint, change from baseline in iADRS at Week 76, compared to placebo in both the low/medium tau population (3.25 [-35.1%], $p < 0.001$) and the overall population (2.92 [-22.3%], $p < 0.001$) (Table 8). Separation from placebo was detected by Week 12, which was nominally statistically significant, and was maintained through Week 76 (Figure 1). MMRM analysis of the primary endpoint provided similar estimates of the treatment effect in the low/medium tau (3.80 [-39.6%], $p < 0.001$) and overall (3.03 [-22.9%], $p < 0.001$) populations.

Table 8: Study AACI Primary Endpoint Analysis

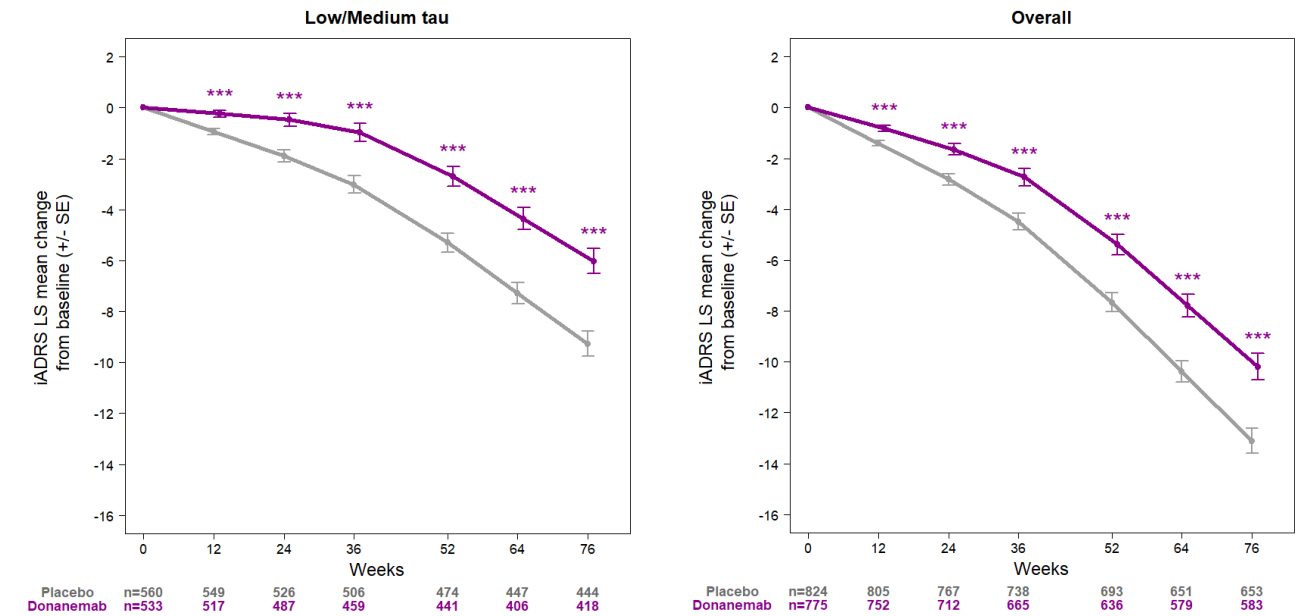
	Low/Medium Tau		Overall	
	Placebo (N=560)	Donanemab (N=533)	Placebo (N=824)	Donanemab (N=775)
Baseline iADRS				
n	560	533	824	775
Mean	105.95	105.92	103.82	104.55

Change from Baseline in iADRS at Week 12				
N	549	517	805	752
Adjusted mean	-0.94	-0.23	-1.41	-0.81
Standard error	0.12	0.13	0.11	0.12
Difference from placebo		0.71		0.60
95% CI for difference		(0.366, 1.053)		(0.277, 0.917)
% difference vs. placebo		-75.4%		-42.3%
p-value (compared with placebo)		<0.001		<0.001
Change from Baseline in iADRS at Week 24				
n	526	487	767	712
Adjusted mean	-1.89	-0.47	-2.83	-1.64
Standard error	0.24	0.25	0.23	0.23
Difference from placebo		1.42		1.19
95% CI for difference		(0.732, 2.102)		(0.554, 1.832)
% difference vs. placebo		-75.1%		-42.2%
p-value (compared with placebo)		<0.001		<0.001
Change from Baseline in iADRS at Week 36				
n	506	459	738	665
Adjusted mean	-3.02	-0.97	-4.48	-2.74
Standard error	0.34	0.35	0.32	0.33
Difference from placebo		2.05		1.74
95% CI for difference		(1.102, 3.008)		(0.841, 2.639)
% difference vs. placebo		-68.0%		-38.8%
p-value (compared with placebo)		<0.001		<0.001
Change from Baseline in iADRS at Week 52				
n	474	441	693	636
Adjusted mean	-5.30	-2.69	-7.66	-5.39
Standard error	0.38	0.39	0.38	0.39
Difference from placebo		2.62		2.27
95% CI for difference		(1.544, 3.686)		(1.205, 3.333)
% difference vs. placebo		-49.3%		-29.6%
p-value (compared with placebo)		<0.001		<0.001
Change from Baseline in iADRS at Week 64				
n	447	406	651	579
Adjusted mean	-7.28	-4.35	-10.38	-7.79
Standard error	0.42	0.43	0.43	0.45
Difference from placebo		2.93		2.59
95% CI for difference		(1.756, 4.111)		(1.388, 3.802)
% difference vs. placebo		-40.3%		-25.0%
p-value (compared with placebo)		<0.001		<0.001
Change from Baseline in iADRS at Week 76				
n	444	418	653	583
Adjusted mean	-9.27	-6.02	-13.11	-10.19

Standard error	0.49	0.50	0.50	0.53
Difference from placebo		3.25		2.92
95% CI for difference		(1.883, 4.618)		(1.508, 4.331)
% difference vs. placebo		-35.1%		-22.3%
p-value (compared with placebo)		<0.001		<0.001

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

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



Created by the reviewer

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

***p<0.001

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

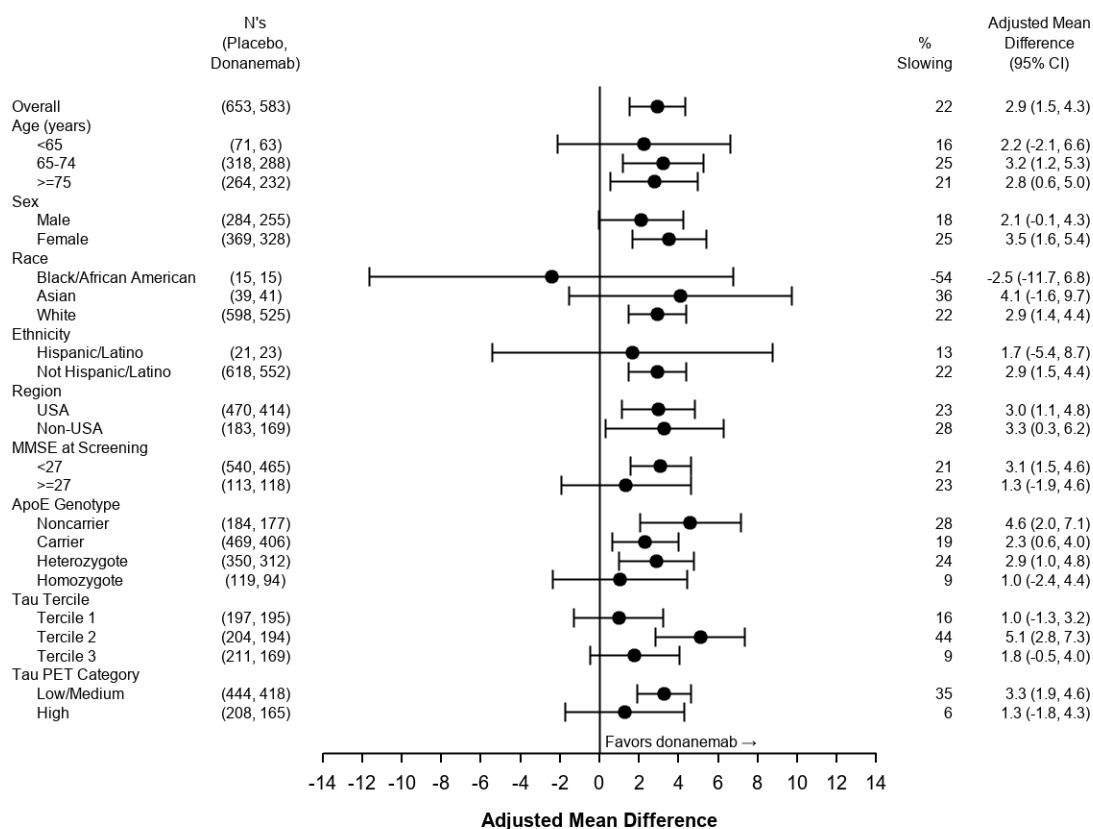
Several sensitivity analyses, including ones requested by the statistical reviewer, demonstrated that the statistically significant results were robust to different modeling assumptions. See Dr. Tran's statistical review for more information.

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

Subgroup Analysis of the Primary Efficacy Endpoint

Results of subgroup analyses in the overall population are provided in Figure 2. With the exception of the small subgroup of Black/African American race, all subgroups favored the donanemab treatment arm compared to placebo. Findings in key subgroups are further discussed in Section 7.1.3.

Figure 2: Subgroup Analysis of the Primary Endpoint in Overall Population



Source: Dr. Tran's statistical review

Data Quality and Integrity

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

Efficacy Results – Secondary clinical endpoints

Statistically significant differences from placebo were observed in the donanemab treatment arm for all multiplicity-controlled secondary clinical endpoints in both the low/medium tau and overall populations.

CDR-SB

Donanemab treatment demonstrated a statistically significant reduction in decline on change from baseline CDR-SB compared to placebo in the low/medium tau population (-0.67 [-36%], $p < 0.001$) and the overall population (-0.70 [-29%], $p < 0.001$) (Table 9). Separation from placebo was detected by Week 24, which was nominally statistically significant, in the low/medium tau population and Week 12 in the overall population and maintained through Week 76 (Figure 3).

Table 9: Study AACI Secondary Endpoint Analysis (CDR-SB, MMRM)

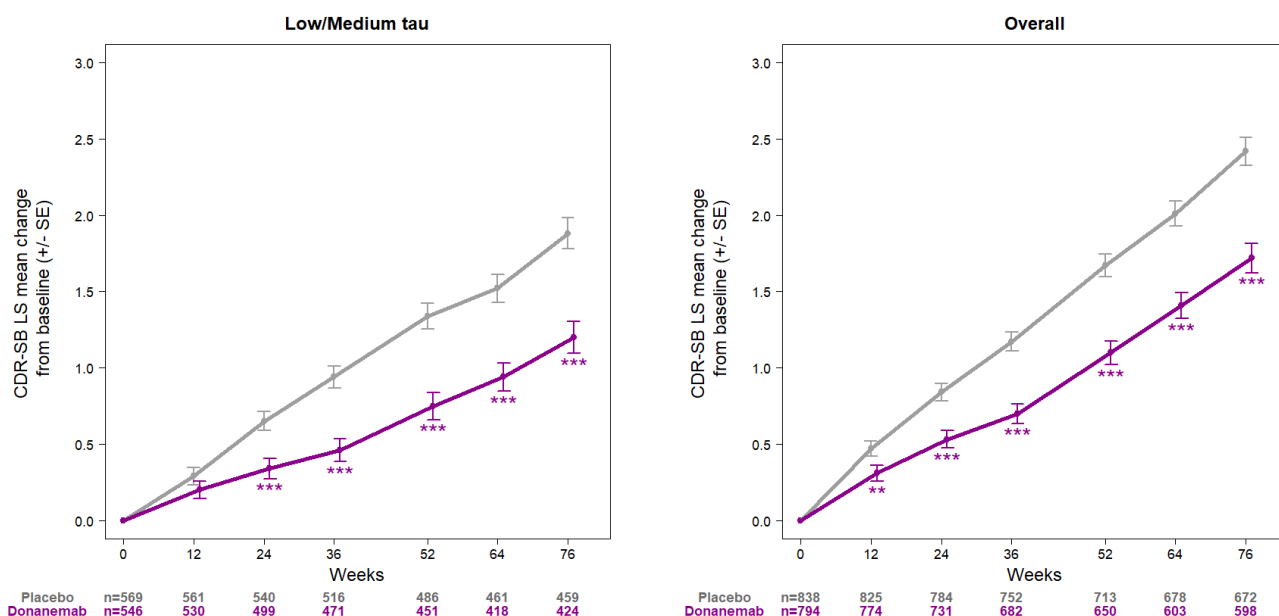
	Low/Medium Tau		Overall	
	Placebo (N=569)	Donanemab (N=546)	Placebo (N=838)	Donanemab (N=794)
Baseline CDR-SB				
N	569	546	838	794
Mean	3.64	3.72	3.89	3.92
Change from Baseline in CDR-SB at Week 12				
N	561	530	825	774
Adjusted mean	0.29	0.20	0.47	0.31
Standard error	0.057	0.059	0.051	0.052
Difference from placebo		-0.10		-0.16
95% CI for difference		(-0.24, 0.04)		(-0.29, -0.04)
% difference vs. placebo		-33.5%		-34.4%
p-value (compared with placebo)		0.167		0.008
Change from Baseline in CDR-SB at Week 24				
n	540	499	784	731
Adjusted mean	0.65	0.34	0.84	0.53
Standard error	0.063	0.066	0.056	0.057
Difference from placebo		-0.31		-0.31
95% CI for difference		(-0.47, -0.14)		(-0.44, -0.17)
% difference vs. placebo		-47.2%		-36.5%
p-value (compared with placebo)		<0.001		<0.001
Change from Baseline in CDR-SB at Week 36				
n	516	471	752	682
Adjusted mean	0.94	0.46	1.17	0.70

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Kevin Krudys, PhD
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Kisunla (Donanemab)

Standard error	0.072	0.074	0.062	0.064
Difference from placebo		-0.48		-0.47
95% CI for difference		(-0.67, -0.29)		(-0.63, -0.31)
% difference vs. placebo		-50.8%		-40.1%
p-value (compared with placebo)		<0.001		<0.001
Change from Baseline in CDR-SB at Week 52				
n	486	451	713	650
Adjusted mean	1.34	0.75	1.67	1.10
Standard error	0.085	0.089	0.075	0.077
Difference from placebo		-0.59		-0.56
95% CI for difference		(-0.82, -0.37)		(-0.76, -0.37)
% difference vs. placebo		-44.4%		-33.8%
p-value (compared with placebo)		<0.001		<0.001
Change from Baseline in CDR-SB at Week 64				
n	461	418	678	603
Adjusted mean	1.52	0.94	2.01	1.41
Standard error	0.090	0.093	0.082	0.085
Difference from placebo		-0.58		-0.60
95% CI for difference		(-0.82, -0.34)		(-0.82, -0.39)
% difference vs. placebo		-38.3%		-30.1%
p-value (compared with placebo)		<0.001		<0.001
Change from Baseline in CDR-SB at Week 76				
n	459	424	672	598
Adjusted mean	1.88	1.20	2.42	1.72
Standard error	0.102	0.105	0.092	0.096
Difference from placebo		-0.67		-0.70
95% CI for difference		(-0.95, -0.40)		(-0.95, -0.45)
% difference vs. placebo		-36.0%		-28.9%
p-value (compared with placebo)		<0.001		<0.001

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

Figure 3: Study AACI Longitudinal Change from Baseline for CDR-SB (left – low/medium tau population, right – overall population)



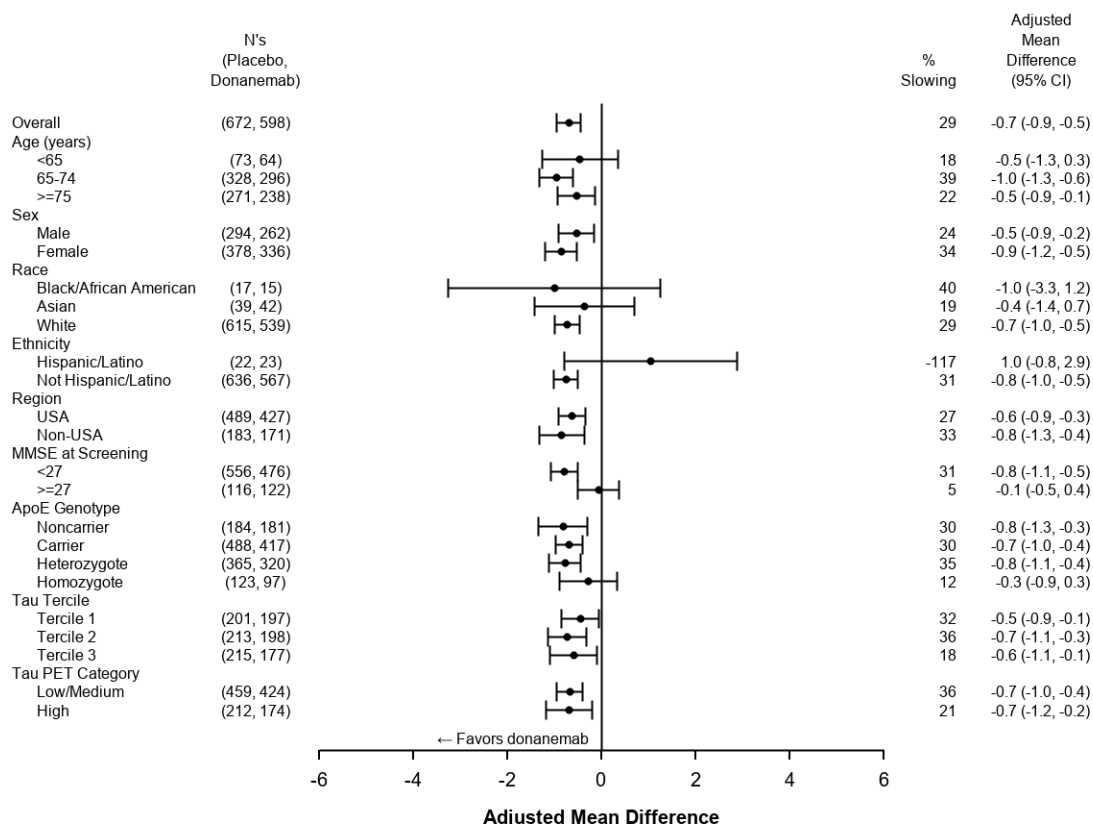
Created by the reviewer
Source: Tables AACI.5.6 and AACI.5.7 from Study AACI CSR
p<0.01, *p<0.001

Sensitivity analyses were performed and demonstrate that the statistically significant results were robust.

The treatment effect on CDR-SB was contextualized in terms of time saved using PMRM. Donanemab treatment resulted in a statistically significant estimate of time saved of 7.53 (5.69, 9.36) months (p<0.001) in the low/medium tau population and 5.44 (3.90, 6.98) months (p<0.001) in the overall population over the 18-month treatment period. Proportional time slowing was assumed in both populations.

The estimate of the treatment effect favored donanemab across all prespecified subgroups of interest except for the small subgroup of Hispanic/Latino ethnicity (Figure 4).

Figure 4: Subgroup Analysis of CDR-SB in Overall Population



Source: Dr. Tran's statistical review
MMRM used by the statistical reviewer for subgroup analysis

ADAS-Cog 13

Donanemab treatment demonstrated a statistically significant reduction in decline on change from baseline ADAS-Cog 13 compared to placebo in the low/medium tau population (-1.52 [-32%], $p < 0.001$) and the overall population (-1.33 [-20%], $p < 0.001$) (Table 10). Separation from placebo was detected by Week 12, which was nominally statistically significant, and maintained through Week 79 (Figure 5).

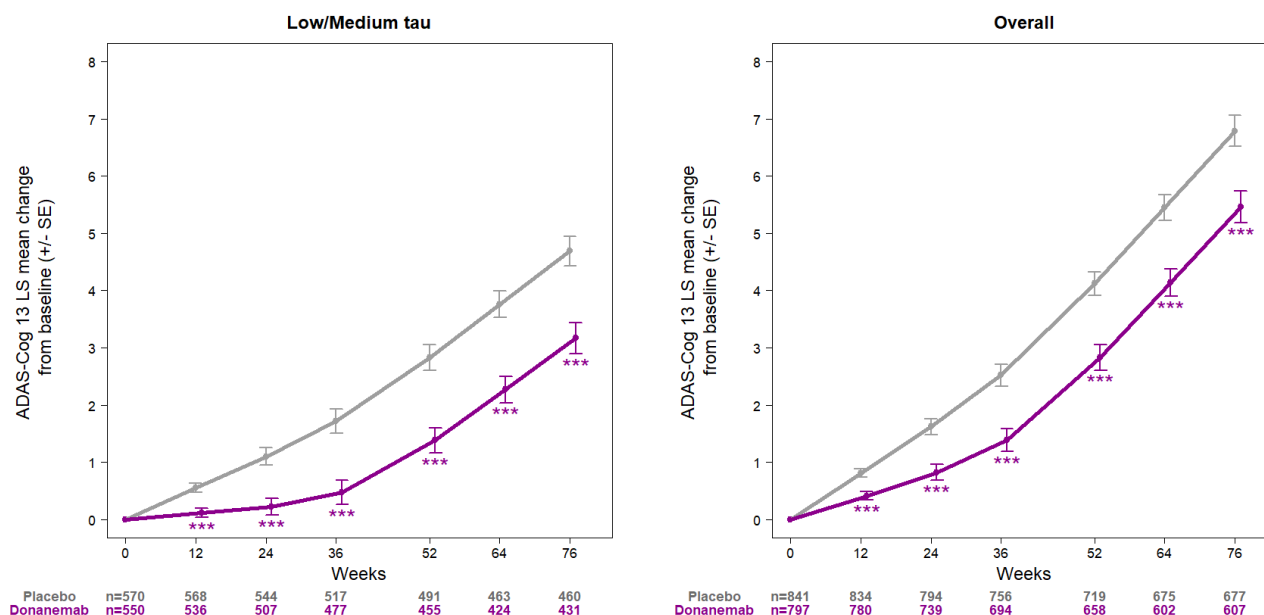
Table 10: Study AACI Secondary Endpoint Analysis (ADAS-Cog 13, NCS)

	Low/Medium Tau		Overall	
	Placebo (N=570)	Donanemab (N=550)	Placebo (N=841)	Donanemab (N=797)
Baseline ADAS-Cog 13				
N	570	550	841	797
Mean	27.60	27.41	29.16	28.53

Change from Baseline in ADAS-Cog 13 at Week 76				
n	460	431	677	607
Adjusted mean	4.69	3.17	6.79	5.46
Standard error	0.26	0.27	0.27	0.28
Difference from placebo		-1.52		-1.33
95% CI for difference		(-2.250, -0.794)		(-2.086, -0.565)
% difference vs. placebo		-32.4%		-19.5%
p-value (compared with placebo)		<0.001		<0.001

Source: Tables AACI.5.8 and AACI.5.9 from Study AACI CSR

Figure 5: Study AACI Longitudinal Change from Baseline for ADAS-Cog 13 (left – low/medium tau population, right – overall population)



Created by the reviewer

Source: Tables AACI.5.8 and AACI.5.9 from Study AACI CSR

p<0.01, *p<0.001

ADCS-iADL

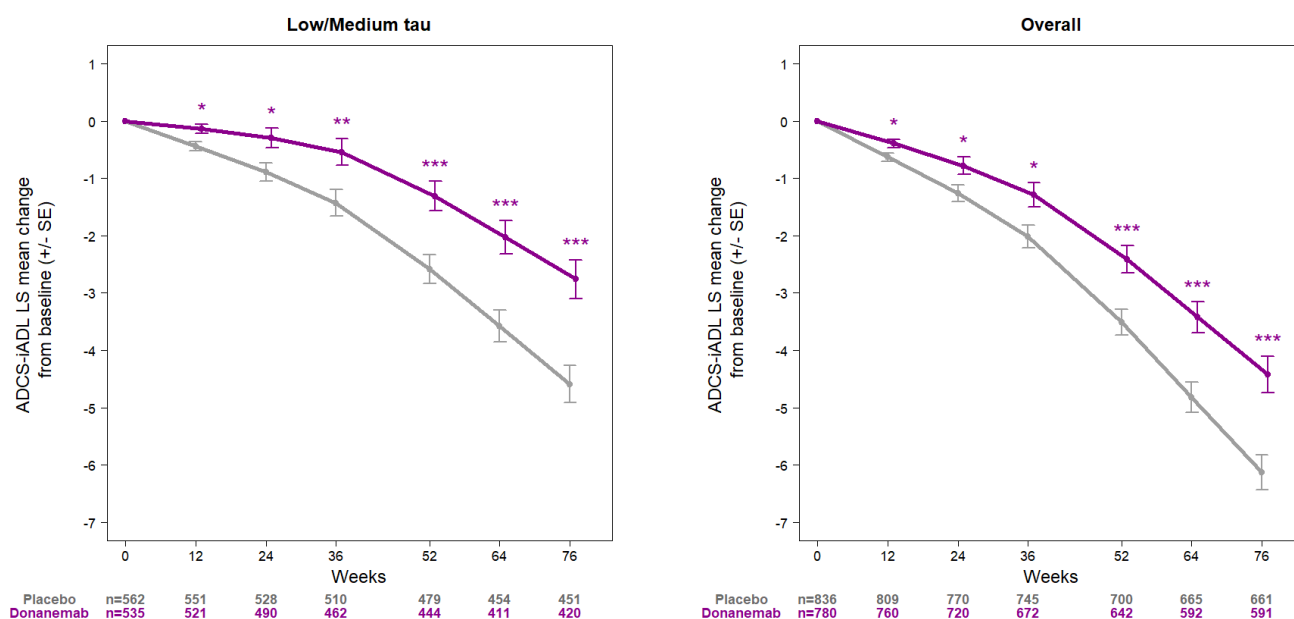
Donanemab treatment demonstrated a statistically significant reduction in decline on change from baseline ADCS-iADL compared to placebo in the low/medium tau population (1.83 [-40%], p<0.001) and the overall population (1.70 [-28%], p<0.001) (Table 11). Separation from placebo was detected by Week 12, which was nominally statistically significant, and maintained through Week 76 (Figure 6).

Table 11: Study AACI Secondary Endpoint Analysis (ADCS-iADL, NCS)

	Low/Medium Tau		Overall	
	Placebo (N=562)	Donanemab (N=535)	Placebo (N=826)	Donanemab (N=780)
Baseline ADCS-iADL				
N	562	535	826	780
Mean	48.56	48.20	47.98	47.96
Change from Baseline in ADCS-iADL at Week 76				
n	451	420	661	591
Adjusted mean	-4.59	-2.76	-6.13	-4.42
Standard error	0.32	0.34	0.30	0.32
Difference from placebo		1.83		1.70
95% CI for difference		(0.913, 2.748)		(0.840, 2.566)
% difference vs. placebo		-39.9%		-27.8%
p-value (compared with placebo)		<0.001		<0.001

Source: Tables AACI.5.10 and AACI.5.11 from Study AACI CSR

Figure 6: Study AACI Longitudinal Change from Baseline for ADCS-iADL (left – low/medium tau population, right – overall population)



Created by the reviewer

Source: Tables AACI.5.10 and AACI.5.11 from Study AACI CSR

*p<0.05, **p<0.01, ***p<0.001

MMSE

MMSE was listed in the protocol as a secondary endpoint but was not included in the statistical testing hierarchy. Results for MMSE showed less change from baseline at Week 76 in the donanemab treatment group than in subjects on placebo in the low/medium tau population (0.48 [-23%], 95% CI [0.09, 0.87]) and the overall population (0.47 [-16%], 95% CI [0.10, 0.84]).

Efficacy Results – Pharmacodynamic Endpoints

Amyloid PET

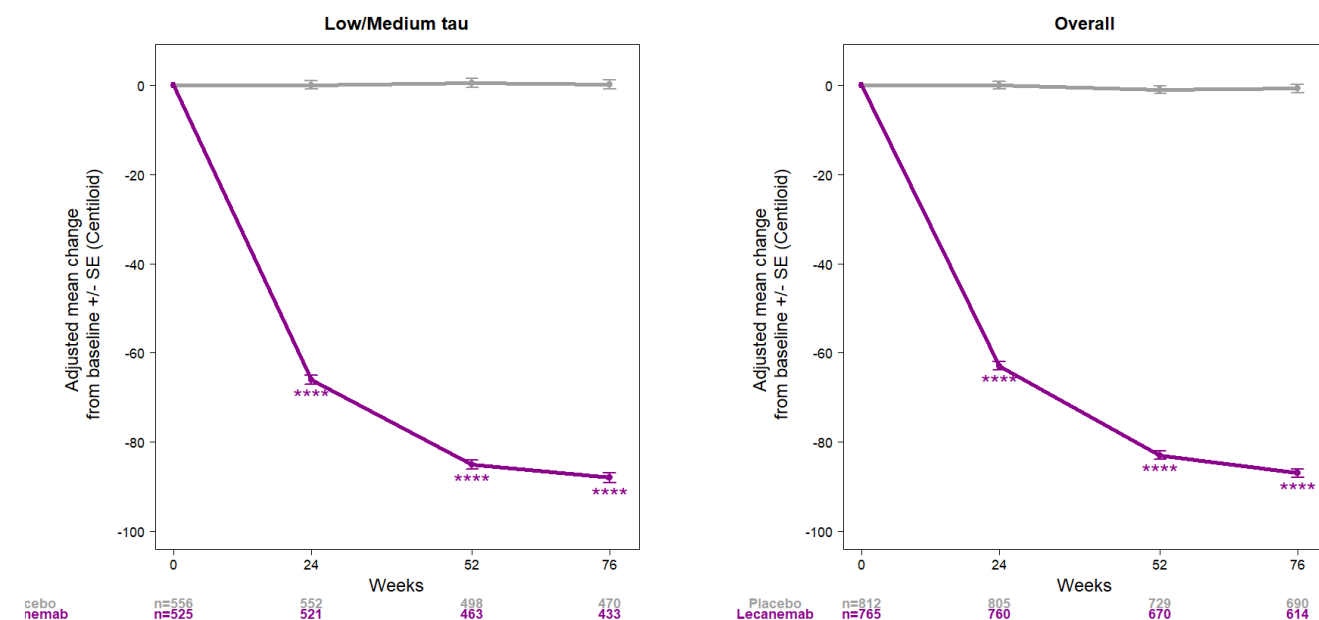
Donanemab treatment demonstrated a statistically significant effect on change from baseline in brain amyloid plaque as measured by PET and reported as Centiloids at Week 76 in the low/medium tau population (-88.2, $p < 0.0001$) and the overall population (-86.4, $p < 0.0001$) (Table 12). The results indicate a time-dependent relationship (Figure 7). In the donanemab treatment arm, 29.7% (226/761), 66.1% (443/670), and 76.4% (469/614) of subjects who had an amyloid PET scan had Centiloid levels less than 24.1 at Weeks 24, 52, and 76, respectively. There were 2 subjects (0.3%) in the placebo arm with Centiloid levels less than 24.1 at Week 76. 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.

Table 12: Study AACI Pharmacodynamic Endpoint Analysis (Amyloid PET)

	Low/Medium Tau		Overall	
	Placebo (N=556)	Donanemab (N=525)	Placebo (N=812)	Donanemab (N=765)
Baseline Centiloid				
N	556	525	812	765
Mean	100.9	103.0	101.8	104.0
Change from Baseline in Centiloid at Week 76				
n	470	433	690	614
Adjusted mean	0.2	-88.0	-0.7	-87.0
Standard error	1.1	1.1	0.9	1.0
Difference from placebo		-88.2		-86.4
95% CI for difference		(-91.2, -85.2)		(-88.9, -83.9)
p-value (compared with placebo)		<0.0001		<0.0001

Source: Tables AACI.8.44 and AACI.8.45 from Study AACI CSR

Figure 7: Study AACI Change from Baseline in Brain Amyloid (left – low/medium tau population, right – overall population)



Created by the reviewer
Source: Tables AACI.8.44 and AACI.8.55 from Study AACI CSR
****p<0.0001

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 (0.002, p=0.97) or the overall population (-0.004, p=0.45). Similarly, no treatment effect was observed in either population in AD-signature-weighted SUVR tau deposition or in exploratory regional (i.e., posterior lateral temporal and parietal) tau endpoints (Table 13).

Table 13: Summary of Tau PET Analysis (Week 76)

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 Study AACI CSR and APP.1.1, APP.1.2, APP.1.3, and APP.1.4 in September 29, 2023, response to information request

vMRI

Donanemab treatment was associated with a decrease in whole brain volume and an increase in ventricular volume at Week 76 (Table 14). Similar changes have been observed with other monoclonal antibodies targeting aggregated brain amyloid. Although it is possible that the findings could represent atrophy, given the favorable results on clinical endpoints observed in Study AACI, the clinical relevance of these changes is unclear. It is also notable that, in contrast to whole brain and ventricular volume changes, there was a trend for a reduction in volume loss in the hippocampus with donanemab treatment.

Table 14: Summary of vMRI Analysis (Week 76)

Baseline (cm³)			LS Mean Change From Baseline (Week 76)		Difference From Placebo (95% CI)
Region	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 Study AACI CSR

Plasma Biomarkers

Donanemab treatment demonstrated a statistically significant effect on change from baseline in plasma p-tau 217 at Weeks 24 and 76 ($p < 0.0001$). Donanemab treatment was also associated with a decrease in p-tau 181 and GFAP compared to placebo at Week 76 (Table 15). Treatment effects were observed by Week 24 for these biomarkers.

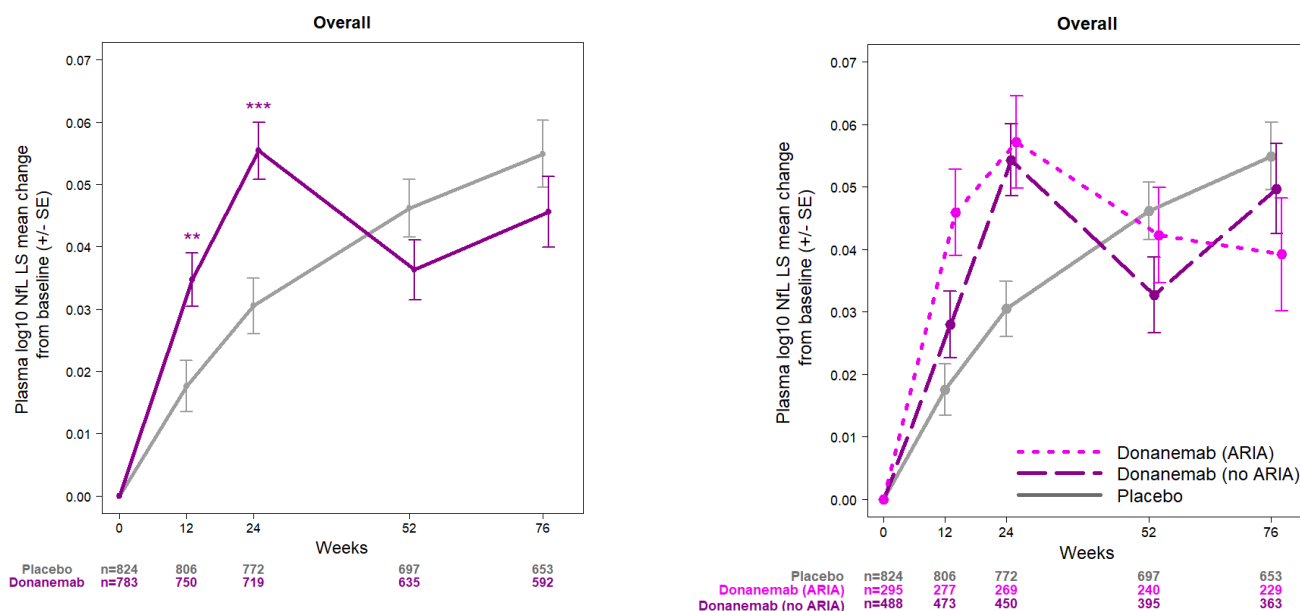
Table 15: Summary of Plasma Biomarker Analyses (Week 76)

Baseline			LS Mean Change from Baseline (Week 76)		Difference from Placebo (95% CI)
Biomarker	Donanemab	Placebo	Donanemab	Placebo	
Low/Medium Tau Population					
log ₁₀ p-tau 217	n=522	n=537	n=395	n=429	-0.25
	0.62	0.59	-0.22	0.04	(-0.28, -0.22)
log ₁₀ p-tau 181	n=530	n=555	n=411	n=445	-0.10
	1.58	1.58	-0.09	0.01	(-0.12, -0.09)
log ₁₀ GFAP	n=538	n=560	n=417	n=451	-0.14
	2.44	2.42	-0.10	0.04	(-0.16, -0.12)
log ₁₀ NfL	n=538	n=560	n=417	n=451	-0.01
	1.31	1.29	0.03	0.05	(-0.03 0.01)
Overall Population					
log ₁₀ p-tau 217	n=758	n=786	n=568	n=620	-0.22
	0.67	0.66	-0.19	0.03	(-0.24, -0.20)
log ₁₀ p-tau 181	n=774	n=813	n=583	n=642	-0.11
	1.60	1.59	-0.08	0.02	(-0.12, -0.10)
log ₁₀ GFAP	n=783	n=824	n=592	n=653	-0.14
	2.44	2.43	-0.09	0.05	(-0.15, -0.12)
log ₁₀ NfL	n=783	n=824	n=592	n=653	-0.01
	1.31	1.31	0.05	0.05	(-0.02, 0.01)

Source: Tables AACI.8.58, AACI.8.59, AACI.8.64, AACI.8.65, AACI.8.60, AACI.8.61, AACI.8.62, and AACI.8.63 from Study AACI CSR

No treatment difference was observed for plasma NfL at Week 76 (Table 15), but a larger increase was observed in the donanemab arm compared to placebo at Weeks 12 and 24. To investigate the potential influence of ARIA on plasma NfL levels, the reviewer performed an analysis of change from baseline of plasma NfL in the donanemab treatment arm by incidence of treatment-emergent ARIA (Figure 8). There was a larger increase in plasma NfL levels at Week 12 in donanemab-treated subjects with treatment-emergent ARIA compared to those without ARIA, but in general the overall pattern over 76 weeks was similar.

Figure 8: Study AAI Change from Baseline in Plasma NFL (left – overall population, right - overall population by incidence of ARIA in donanemab arm)



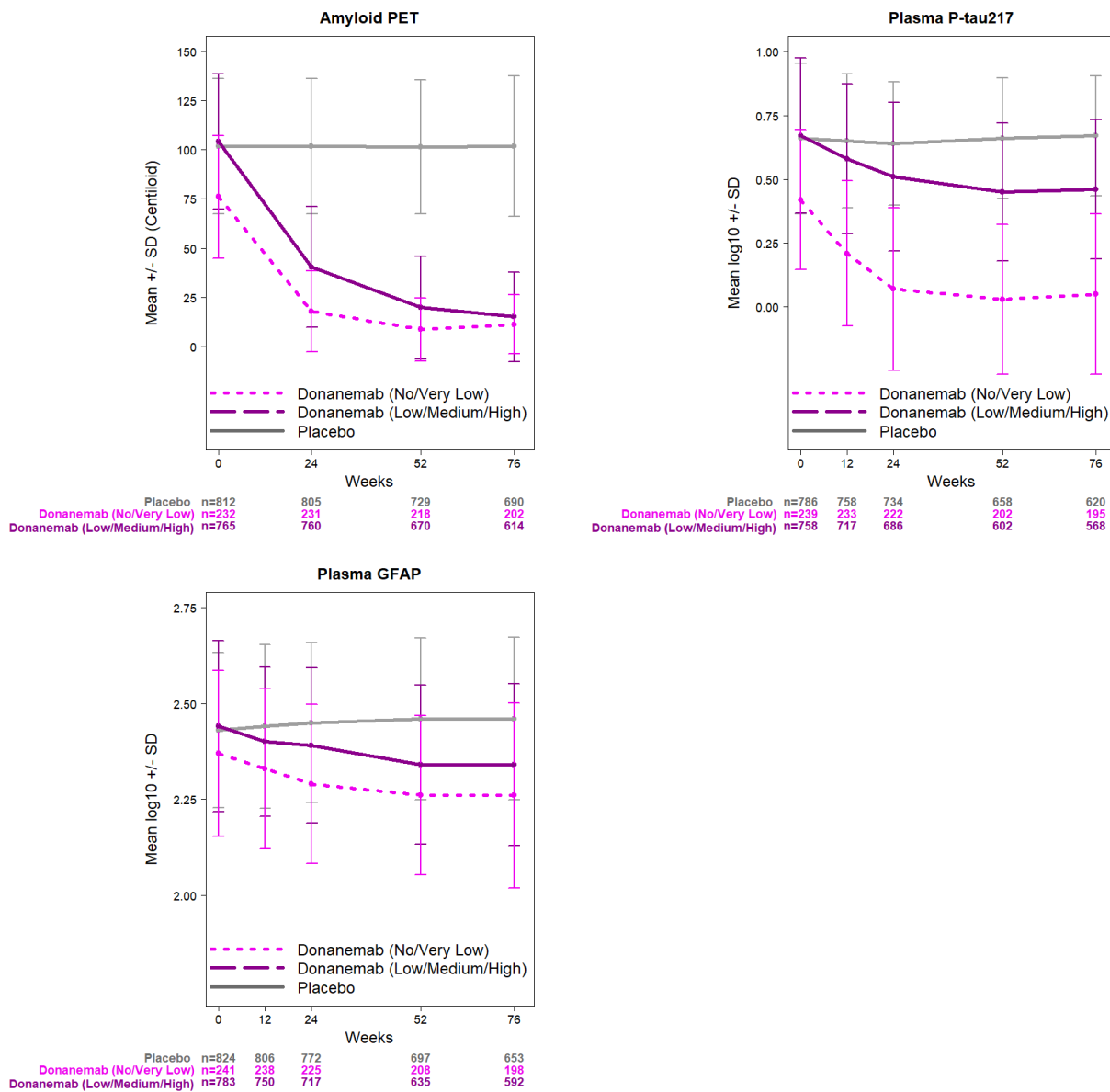
Created by the reviewer

Source: (left) Tables AACI.8.63 from Study AACI CSR; (right) created by reviewer using adnfl.xpt and adsl.xpt

p<0.01, *p<0.001

Biomarker results in the subjects with no or very low tau enrolled in the safety addendum are presented in Figure 9 and compared to biomarker results in the donanemab treatment arm from Study AACI. Subjects with no or very low tau had lower baseline values, but the reductions from baseline were generally consistent with that observed in subjects with low/medium and high tau.

Figure 9: Biomarker Results in Subjects with No or Very Low Tau (Study AACI Safety Addendum) Compared to Subjects with Low/Medium/High Tau (Study AACI)



Created by the reviewer

Source: adgfap.xpt, adept.xpt, adptau.xpt, and adsl.xpt in 11/21/2023 regulatory response

Efficacy Results – Exploratory Efficacy Endpoints

DSST

No treatment effect was observed for the DSST in either the low/medium tau or overall population (Table 16).

Table 16: Summary of DSST Analysis

Endpoint	Baseline		LS Mean Change From Baseline (Week 76)		Difference From Placebo (95% CI)
	Donanemab	Placebo	Donanemab	Placebo	
Low/Medium Tau Population					
	n=495	n=531	n=373	n=408	
DSST	26.55	25.69	-6.40	-5.99	-0.40 (-1.58, 0.77)
Overall Population					
	n=716	n=766	n=502	n=569	
DSST	24.15	23.22	-7.09	-7.04	-0.05 (-1.04, 0.94)

Source: Tables AACI.8.68 and AACI.8.69 from Study AACI CSR

Time to Substantial Decline

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

Donanemab treatment also reduced the risk of progression on the CDR-SB (≥ 1 point increase for subjects with MMSE at screening of 27-30 or ≥ 2 points increase for subjects with MMSE at screening of 20-26) by 40% with a hazard ratio of 0.60 (0.47, 0.75) in the low/medium tau population and by 38% with a hazard ratio of 0.62 (0.52, 0.75) in the overall population. Similarly, the risk of progression on the iADRS (5 points decrease in iADRS for subjects with MMSE at screening of 27-30 or 9 points decrease for subjects with MMSE at screening of 20-26) was reduced with donanemab treatment by 36% with a hazard ratio of 0.64 (0.51, 0.81) in the low/medium tau population and by 30% with a hazard ratio of 0.70 (0.58, 0.84) in the overall population.

Responder Analysis

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

Dose/Dose Response

A dose-response relationship was not observed because only a single dosing regimen was included in the study. Greater amyloid plaque reduction was associated with higher doses of donanemab in the single- and multiple-ascending dose study (AACD). See the clinical pharmacology review for further information, including evaluation of exposure-response relationships.

Durability of Response

Statistically significant treatments effects for the primary and secondary endpoints were generally observed by the 3-month visit, and the absolute treatment difference tended to increase over time for the 18 months of the placebo-controlled portion of the study. Amyloid plaque continued to decline to levels consistent with amyloid negativity by visual read on PET imaging following dosing with donanemab. It is anticipated that with a drug that impacts the underlying disease biology that the treatment benefit will increase over time and that is, in fact, what was demonstrated in Study AACI over 76 weeks. Durability of response for a longer period of time may be addressed when data from the long-term extension portion of the study become available.

Persistence of Effect

Study AACI was not designed to address the effect of donanemab after treatment is stopped or withheld. There were a number of donanemab-treated subjects who had their dose reduced to placebo during the study based on amyloid PET results, but data from these subjects are inadequate to draw conclusions regarding persistence of effect on clinical endpoints due to the relatively short off-treatment period, the lack of an appropriate comparator group, and the fact that donanemab continues to exert a pharmacodynamic effect after dose cessation. 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 may be reasonable, there is still some uncertainty about the appropriate threshold, and the assumption was not verified by including an arm with continuous donanemab dosing. Data from the ongoing long-term extension portion of the study or from the ongoing Study AACM in preclinical Alzheimer's disease may provide insight into the persistence of effect.

Using data from patients who completed active treatment based on amyloid imaging, amyloid levels began to increase with a mean rate of 2.8 Centiloids/year. Data suggest that re-accumulation of plasma markers may occur at a faster rate than amyloid plaque on PET (see Figure 9 in Dr. Nookala's clinical pharmacology review). Although re-accumulation of amyloid plaque is relatively slow at the mean level, the potential for re-initiation of donanemab based on amyloid levels remains uncertain and untested.

6.2. Study AACG (I5T-MC-AACG) Assessment of Safety, Tolerability, and Efficacy of LY3002813 in Early Symptomatic Alzheimer's Disease

Study AACG, a smaller Phase 2 study, was reviewed during the original submission for accelerated approval (Krudys, DARRTS 1/17/2023) and will only be briefly summarized here.

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

The primary efficacy endpoint analysis of change from baseline in iADRS at Week 76 demonstrated a statistically significant treatment effect in the donanemab treatment arm compared to placebo (3.2; 95% CI 0.1, 6.3; $p=0.04$; 32% reduction). The difference between the donanemab group and the placebo group in the change from baseline in CDR-SB at Week 76 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).

7. Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

7.1.1. Primary Endpoints

The primary endpoint in Studies AACG and AACI was the change from baseline in iADRS at Week 76. Studies AACG and AACI shared many design characteristics and enrolled a similar patient population with early Alzheimer's disease. The main differences between the studies were: (1) AACG was a smaller Phase 2 study enrolling approximately 15% the number of subjects of Study AACI, (2) Study AACG only enrolled subjects with low/medium tau load on tau PET whereas Study AACI also allowed enrollment of subjects with high tau load, (3) both studies allowed down titration to placebo, but Study AACG included down titration to 700 mg donanemab, and (4) Study AACI included fewer protocol-mandated dosing restrictions based on ARIA. The most direct comparison for Study AACG is the low/medium tau population from

Study AACI.

A summary of the results for iADRS across the two studies is displayed in Table 17. The statistically significant result in favor of donanemab in Study AACI is consistent with the result from Study AACG. The magnitude of the effect is also remarkably consistent in the low/medium tau populations in the two studies. The smaller magnitude of the treatment effect estimate in the overall population in Study AACI provides support for the applicant's hypothesis that an earlier population with less tau pathology is more likely to respond to donanemab.

Table 17: Summary of Findings for iADRS in Studies AACG and AACI

	Study AACG (Low/Medium tau)		Study AACI			
	Placebo	Donanemab	Low/Medium tau		Overall	
	Placebo	Donanemab	Placebo	Donanemab	Placebo	Donanemab
N, Randomized population	126	131	594	588	876	860
n at Week 76	91	93	444	418	653	583
Baseline	106.06	106.30	105.95	105.92	103.82	104.55
Change from baseline (Week 76)	-10.06	-6.86	-9.27	-6.02	-13.11	-10.19
Difference from placebo (%)		3.20 (-32%)		3.25 (-35%)		2.92 (-22%)
p-value		0.042		<0.001		<0.001

Source: Tables AACI.5.2 and AACI.5.3 from Study AACI CSR and Table AACG.5.1 from Study AACG CSR.

In the March 2, 2021, Type C Meeting minutes, the Division did not agree that a statistically significant treatment effect on the iADRS, unaccompanied by a valid statistically significant treatment effect on its two components was acceptable for use as a primary efficacy assessment. The Division also was not persuaded that an effect on the iADRS could be considered necessarily clinically meaningful or reflective of effects on each of its individual components. However, Study AACI demonstrated statistically significant changes on both the ADAS-Cog 13 and the ADCS-iADL components of the scale (see discussion in Section 7.1.2). In Study AACG, there were numerical trends on both the ADAS-Cog 13 and ADCS-iADL components that were consistent with those observed in AACI that did not reach statistical significance.

7.1.2. Secondary and Other Endpoints

The disagreement over the choice of iADRS as the primary endpoint is mostly inconsequential because positive results were also observed for the CDR-SB and both components of the iADRS, ADAS-Cog 13 and the ADCS-iADL, which were secondary endpoints in Study AACI. These secondary endpoints encompass two acceptable approaches suggested by the Division to the applicant: (1) CDR-SB or (2) ADAS-Cog 13 and ADCS-iADL as coprimary endpoints.

Results for CDR-SB in the two studies are presented in Table 18. CDR-SB was the first ranked secondary endpoint in both studies. The treatment effect did not reach statistical significance in Study AACG, but the estimate of the treatment effect was consistent with that observed in Study AACI. The statistically significant results for iADRS in Study AACG, but not CDR-SB may suggest that iADRS is a more sensitive measure appropriate for smaller studies. The statistically significant results with low p-values in Study AACI for both endpoints suggest that large pivotal studies may not be sensitive to the choice of endpoint.

Table 18: Summary of Findings for CDR-SB in Studies AACG and AACI

	Study AACG (<i>Low/Medium tau</i>)		Study AACI			
	Placebo	Donanemab	<i>Low/Medium tau</i>		<i>Overall</i>	
			Placebo	Donanemab	Placebo	Donanemab
N, Randomized population	126	131	594	588	876	860
n at Week 76	90	93	459	424	672	598
Baseline	3.37	3.55	3.64	3.72	3.89	3.92
Change from baseline (Week 76)	1.58	1.22	1.88	1.20	2.42	1.72
Difference from placebo (%)		-0.36 (-23%)		-0.67 (-36%)		-0.70 (-29%)
p-value		0.14		<0.001		<0.001

Source: Tables AACI.5.7 and AACI.5.6 from Study AACI CSR and Table AACG.5.2 from Study AACG CSR.

The effect on CDR-SB represents a clinically meaningful reduction in clinical decline. The magnitude of effect is consistent with what has been observed in trials of other therapies which reduce brain amyloid to levels consistent with a negative PET scan.

Results for ADAS-Cog 13 and ADCS-iADL are presented in Table 19 and Table 20, respectively. Statistically significant effects on ADAS-Cog 13 and ADCS-iADL in Study AACI, endpoints which independently assess cognition and daily function, represent an acceptable co-primary approach in Alzheimer's disease. The results for these endpoints in Study AACG are generally

consistent with those from Study AACI but did not reach statistical significance according to the pre-specified analysis plan.

Table 19: Summary of Findings for ADAS-Cog 13 in Studies AACG and AACI

	Study AACG (<i>Low/Medium tau</i>)		Study AACI			
			<i>Low/Medium tau</i>		<i>Overall</i>	
	Placebo	Donanemab	Placebo	Donanemab	Placebo	Donanemab
N, Randomized population	126	131	594	588	876	860
n at Week 76	93	93	460	431	677	607
Baseline	27.53	27.68	27.60	27.41	29.16	28.53
Change from baseline (Week 76)	4.77	2.91	4.69	3.17	6.79	5.46
Difference from placebo (%)		-1.86 (-39%)		-1.52 (-32%)		-1.33 (-20%)
p-value		0.04*		<0.001		<0.001

Source: Tables AACI.5.8 and AACI.5.9 from Study AACI CSR and Table AACG.5.3 from Study AACG CSR.

*nominal p-value

Table 20: Summary of Findings for ADCS-iADL in Studies AACG and AACI

	Study AACG (<i>Low/Medium tau</i>)		Study AACI			
			<i>Low/Medium tau</i>		<i>Overall</i>	
	Placebo	Donanemab	Placebo	Donanemab	Placebo	Donanemab
N, Randomized population	126	131	594	588	876	860
n at Week 76	91	93	451	420	661	591
Baseline	48.58	48.98	48.56	48.20	47.98	47.96
Change from baseline (Week 76)	-5.20	-3.98	-4.59	-2.76	-6.13	-4.42
Difference from placebo (%)		1.21 (-23%)		1.83 (-40%)		1.70 (-28%)
p-value		0.23*		<0.001		<0.001

Source: Tables AACI.5.10 and AACI.5.11 from Study AACI CSR and Table AACG.5.4 from Study AACG CSR.

*nominal p-value

To some extent, each of the secondary clinical endpoints captures distinct information regarding cognitive decline and warrants inclusion in labeling.

Donanemab treatment reduced brain amyloid as measured by PET by a similar extent in both Study AACG and Study AACI (Table 21). Reduction in brain amyloid as measured by PET is a surrogate endpoint that has been found reasonably likely to predict clinical benefit in some AD drug approvals. In the context of the current review for traditional approval, this reduction in brain amyloid provides supportive evidence for the observed effects on clinical endpoints.

Table 21: Summary of Findings for Amyloid PET in Studies AACG and AACI

	Study AACG (Low/Medium tau)		Study AACI			
			Low/Medium tau		Overall	
	Placebo	Donanemab	Placebo	Donanemab	Placebo	Donanemab
N, Randomized population	126	131	594	588	876	860
n at Week 76	91	90	470	433	690	614
Baseline	103.09	107.18	100.941	103.00	101.75	104.02
Change from baseline (Week 76)	0.93	-84.13	0.18	-88.03	-0.67	-87.03
Difference from placebo		-85.06		-88.21		-86.37
p-value		<0.001		<0.001		<0.001

Source: Tables AACI.8.44 and AACI.8.45 from Study AACI CSR and Table AACG.5.8 from Study AACG CSR.

7.1.3. Subpopulations

Subpopulation results for Study AACI are presented in Figure 2 and Figure 4, for iADRS and CDR-SB, respectively. With the exception of the small subgroups of Black/African American race for iADRS and Hispanic/Latino ethnicity for CDR-SB, findings are generally consistent with the overall population estimate and favor treatment with donanemab. Pooled data is not presented because Study AACI has a sufficient number of subjects to support meaningful conclusions for relevant subgroups.

Baseline Tau Levels

Further consideration of efficacy across the spectrum of baseline tau levels is relevant because tau PET imaging was used as an enrichment strategy in Studies AACG and AACI. The applicant does not propose a requirement for confirmation or quantification of tau pathology in the prescribing information despite excluding subjects with no or very low tau from the controlled

portions of Studies AACG and AACI and prioritizing a low/medium tau population in the statistical analysis of Study AACI.

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

The decision to exclude subjects with no or very low tau from Studies AACG and AACI was based on research conducted by the applicant demonstrating that subjects 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 subjects with more advanced tau deposition (Qian et al. 2017). Therefore, tau burden served as a prognostic biomarker to reduce the number of non-progressors enrolled in the studies, and exclusion of subjects 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 clinical efficacy data in subjects with no or very low tau, there is biomarker data from a single-arm, open-label, safety addendum to Study AACI. This addendum included a cohort of subjects who failed the tau PET entry criterion for entry into the double-blind portion of the study. Compared to subjects with low/medium or high tau enrolled in Study AACI, subjects with no or very low tau had lower baseline levels of key biomarkers, consistent with their earlier disease stage. Reductions from baseline were generally similar in the two populations (Figure 9).

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. The primary results of Study AACI in the low/medium and overall populations appear to support these expectations. Nevertheless, the prespecified subgroup analyses by baseline tau tercile (Figure 2 and Figure 4) suggest that a treatment effect was observed across the range of baseline tau levels included in Study AACI, including in subjects with high tau levels. Patients with no or very 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 trial such as Study AACI. The applicant also performed an analysis to explore the relationship between tau levels and efficacy by including baseline tau SUVR, baseline tau SUVR-by-visit, and baseline tau SUVR-by-treatment-by-visit interactions in the original MMRM model described in the statistical analysis plan. Greater relative treatment effects (i.e., percent slowing) were estimated with decreasing baseline tau levels over the range of tau SUVR in the study. This analysis suggests that the benefits of donanemab may be greater in patients in earlier stages of disease with lower tau burden.

It is also important to note that the incidence of ARIA was similar or possibly less in subjects with no or very low tau compared to subjects with high tau (please refer to the safety review by Dr. Branagan).

In conclusion, higher levels of tau on PET imaging were used as a strategy to enrich for subjects who were more likely to progress during the 18-month study. Subjects who meet criteria for Alzheimer's disease based on confirmed presence of brain amyloid and cognitive impairment have the same underlying pathophysiology of disease regardless of the tau burden. The course of the disease is also progressive for all tau levels, although a higher tau burden reflects a later stage of disease that may progress more rapidly. The pharmacodynamic effect of the drug is expected to be similar in patients who are amyloid positive, regardless of tau status, and in fact subjects with no or very low tau treated during the safety addendum showed similar reduction in amyloid plaque on PET and on other pharmacodynamic markers as those with higher tau levels. Furthermore, modeling suggests that clinical benefit may be even greater in patients with lower tau burden. Safety was similar across the spectrum of tau burden. Based on these considerations, it is 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.

7.1.4. Dose and Dose-Response

See Section 6.1.2

7.1.5. Onset, Duration, and Durability of Efficacy Effects

See Section 6.1.2

7.2. Additional Efficacy Considerations

7.2.1. Considerations on Benefit in the Postmarket Setting

The population enrolled in Studies AACG and AACI did not include patients at either end of the Alzheimer's disease continuum (Stage 1-2 or Stage 5-6 as defined by the 2024 FDA Draft Guidance for Early Alzheimer's Disease) and there is some uncertainty with respect to the generalizability of benefit across the entire spectrum of Alzheimer's disease. However, there is a general expectation, and the scientific evidence to date supports, that initiating treatment with donanemab earlier in the disease may provide the best opportunity to delay or halt the pathophysiological processes that lead to the clinical deficits of Alzheimer's disease. The ongoing study (AACM) of donanemab in individuals at risk for cognitive and function decline of Alzheimer's disease should address the potential benefit in this population. Intervention with donanemab later in the disease may be expected to provide less benefit, as downstream pathological processes may dominate.

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

An important consideration for the use of donanemab is that dosing was stopped once amyloid levels were reduced below a certain quantitative threshold on PET imaging. Although subjects continued to show benefit compared to placebo after dosing was stopped, the follow up period is relatively short and there is no information on whether subjects would have shown greater benefit if they had continued dosing. It was shown that amyloid plaques can re-accumulate at low rates following the cessation of therapy. There remains uncertainty regarding the optimal treatment regimen for donanemab once amyloid levels have been reduced to a level that corresponds with a "negative" visual read on PET. Labeling should reflect the uncertainties regarding the optimal duration of treatment. This residual uncertainty also warrants a postmarketing study of the effectiveness of donanemab in subjects who have completed treatment based on amyloid plaque levels and the potential need for re-initiation of treatment or a maintenance regimen to maintain the reduction of amyloid plaque.

7.3. Integrated Assessment of Effectiveness

The evidence submitted in support of effectiveness is derived from randomized, double-blind, placebo-controlled clinical trials of donanemab in patients at the early stages of symptomatic Alzheimer's disease.

Study AACI is an adequate and well-controlled, large multicenter trial with positive and statistically very persuasive results on the primary endpoint, iADRS, and on all multiplicity-controlled secondary clinical endpoints (CDR-SB, ADAS-Cog 13 and ADCS-iADL). These secondary endpoints partly capture distinct information regarding cognitive decline and impact on daily function and support the overall clinical meaningfulness of the results. The treatment effect was apparent by the 3-month visit and the absolute treatment difference tended to increase with time. The robustness of the observed treatment effect was demonstrated by sensitivity analyses, including one assessing the potential for functional unblinding. The treatment effect in Study AACI is supported by the consistently favorable results for the primary and secondary endpoints across subgroups of interest defined by demographic and baseline disease characteristics. Biomarkers reflecting brain amyloid plaque load and astrocytic activation support the observations on the clinical endpoints.

It is useful to interpret treatment difference as a percent reduction rather than the absolute point difference which depends on the length of the study and the disease stage. The results of Study AACI demonstrate a reduced decline of approximately 20% to 30% on clinical endpoints in the combined population. For CDR-SB, this corresponds to a preservation of CDR-SB by approximately 5.4 months relative to placebo over the 18 months of the study. This preservation of cognitive function is clearly clinically meaningful. Further context is provided by the analysis demonstrating a 37% reduction in the risk of progression on the global CDR score and the higher responder rate (CDR-SB change from baseline ≤ 0) for subjects treated with donanemab.

Study AACG is a smaller adequate and well-controlled study which achieved statistical significance on the primary endpoint, iADRS. Despite not reaching statistical significance according to the prespecified hierarchy, the estimates of the treatment effect at Week 76 across secondary endpoints are consistent with the reduction of clinical decline observed in Study AACI. The effect of donanemab on brain amyloid plaque demonstrated in Study AACG was robust and persuasive and supported the design of Study AACI. The results of Study AACG provide independent substantiation for the benefits observed in Study AACI.

8. Review of Safety

Please see the separate safety review by Dr. Branagan.

9. Advisory Committee Meeting and Other External Consultations

An advisory committee meeting was held on June 10, 2024, to discuss whether the data from Study AACI support a favorable benefit-risk assessment for the use of donanemab for the treatment of Alzheimer's disease.

The committee discussed whether the available data provided evidence of effectiveness of donanemab for the treatment of Alzheimer's disease and commented on the support for effectiveness across tau PET subgroups, including the no/very low tau population that was excluded from the placebo-controlled trials. The committee voted unanimously, 11-0, that the data show that donanemab is effective for the treatment of Alzheimer's disease. Most committee members thought biomarker effects in patients enrolled in the Study AACI safety addendum supported efficacy in patients with no or very low tau. There was also general consensus that requiring tau PET would be impractical to implement and would impede access to treatment.

The committee also discussed the dosing regimen used in the clinical trials and if there were scientific and/or clinical considerations that may factor into a decision to stop or continue dosing with donanemab. The committee members agreed that the dosing regimen guided by reduction of amyloid plaque on PET imaging was an innovative component of the clinical trial design that could provide potential benefits for compliance and reduced burden on patients and the health care system. However, members were in agreement that more long-term data is needed to address questions on duration of amyloid clearance, how frequently patients would need to be monitored after stopping donanemab, when treatment should be re-initiated, and potential adverse effects of stopping and restarting therapy.

The committee also discussed the overall risk-benefit of donanemab and voted unanimously, 11-0, that the benefits of donanemab outweigh its risks for the treatment of Alzheimer's disease.

10. Labeling Recommendations

10.1. Prescription Drug Labeling

Edits to the prescribing information have been proposed, but the labeling has not been finalized

at the time of this review.

10.2. Nonprescription Drug Labeling

Not applicable.

11. Risk Evaluation and Mitigation Strategies (REMS)

Please see the separate safety review by Dr. Branagan for considerations regarding a REMS.

12. Postmarketing Requirements and Commitments

A postmarketing commitment to evaluate the long-term efficacy of dose cessation, including the potential need for maintenance dosing, is recommended.

13. Appendices

13.1. References

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13.2. Financial Disclosure

Clinical Review
Kevin Krudys, PhD
BLA 761248 Resubmission
Kisunla (Donanemab)

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

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: <u>>2250</u>		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>4</u>		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: <u>4</u> Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in _____ Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>0</u>		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

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

/s/

KEVIN M KRUDYS
07/01/2024 04:44:12 PM

Clinical Review
Natalie Branagan, MD
BLA 761248
Kisunla/donanemab

CLINICAL REVIEW

Application Type	BLA
Application Number(s)	761248
Priority or Standard	Class 2 resubmission
Submit Date(s)	June 12, 2023
Received Date(s)	June 12, 2023
PDUFA Goal Date	March 12, 2024
Division/Office	DN 1/ON
Reviewer Name(s)	Natalie Branagan, MD
Review Completion Date	June 28, 2024
Established/Proper Name	Donanemab
(Proposed) Trade Name	Kisunla
Applicant	Eli Lilly and Company
Dosage Form(s)	Injection, intravenous
Applicant Proposed Dosing Regimen(s)	700 mg as an intravenous infusion over four weeks for the first 3 doses, followed by 1400 mg every four weeks
Applicant Proposed Indication(s)/Population(s)	Treatment of Alzheimer's disease. Treatment with KISUNLA should be initiated in patients with mild cognitive impairment or mild dementia stage of disease, the population in which treatment was initiated in the clinical trials
Recommendation on Regulatory Action	If efficacy is demonstrated and the benefits of donanemab outweigh the risks, then I recommend approval include appropriate labeling language to address adverse reactions of concern.
Recommended Indication(s)/Population(s) (if applicable)	Indicated for the treatment of early Alzheimer's disease, including patients with mild cognitive impairment and mild Alzheimer's dementia

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Glossary

AC	advisory committee
AE	adverse event
AR	adverse reaction
ARIA	Amyloid related imaging abnormality
ARIA-E	Amyloid related imaging abnormality-edema
ARIA-H	Amyloid related imaging abnormality-microhemorrhages and hemosiderin deposition
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Council for Harmonization
IND	Investigational New Drug Application
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities

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MITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information or package insert
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	system organ classes
TEAE	treatment emergent adverse event

1. Executive Summary

1.1. Product Introduction

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

1.2. Conclusions on the Substantial Evidence of Effectiveness

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

1.3. Benefit-Risk Assessment

Please refer to the Summary Memo.

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Benefit-Risk Dimensions

APPEARS THIS WAY ON ORIGINAL

1.4. Patient Experience Data

Please refer to the review of clinical efficacy by Dr. Kevin Krudys.

2. Therapeutic Context

2.1. Analysis of Condition

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

2.2. Analysis of Current Treatment Options

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

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

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

3.2. Summary of Presubmission/Submission Regulatory Activity

The Applicant submitted BLA 761248 on May 18, 2022, and on January 18, 2022, received a complete response letter from the Division, based on an insufficient safety database to characterize the long-term safety of donanemab. The Division had expected the BLA submission to have at least 100 subjects exposed to drug for ≥ 12 months, consistent with ICH E1 guidelines, to adequately characterize the safety of donanemab. The BLA submission contained data for 49 subjects who were exposed to donanemab at the highest proposed dosage regimen (700 mg for 3 doses followed by 1400 mg thereafter) for 12 months. Additionally, it was noted that the majority of the 6-month safety exposures were from uncontrolled data from open-label studies.

The contents of this resubmission contain the unblinded controlled data from the Phase 3 Study AACI.

The reader is referred to the review of clinical efficacy by Dr. Kevin Krudys for further details of presubmission/submission regulatory activity.

3.3. Foreign Regulatory Actions and Marketing History

There is no foreign marketing experience.

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

4.1. Office of Scientific Investigations (OSI)

The reader is referred to the OSI review.

4.2. Product Quality

The reader is referred to the Product Quality review.

4.3. Clinical Microbiology

Not applicable.

4.4. Nonclinical Pharmacology/Toxicology

The reader is referred to the Nonclinical Pharmacology review.

4.5. Clinical Pharmacology

The reader is referred to the Clinical Pharmacology review.

4.6. Devices and Companion Diagnostic Issues

Not applicable.

4.7. Consumer Study Reviews

Not applicable.

5. Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

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

5.2. Review Strategy

The clinical review of BLA 761248 is divided into a review of clinical efficacy (by Dr. Kevin Krudys) and this review of clinical safety. Information submitted as part of BLA 761248 and published literature are discussed in this review. This reviewer will primarily present analyses conducted by herself and by Senior Clinical Analyst Dr. Rui Li. The primary safety review presented here will focus on Study AACG and the placebo-controlled period of Study AACI, to reflect the safety in the studies that are the primary sources of evidence of effectiveness. The long-term extension period of Study AACI, the Safety Addendum of Study AACI, and Studies AACH Part B, and AACN-Dona Cohort will provide supportive information.

6. Review of Relevant Individual Trials Used to Support Efficacy

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

7. Integrated Review of Effectiveness

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

8. Review of Safety

8.1. Safety Review Approach

The safety population was defined as all subjects who were randomized and received at least one dose of study drug.

Data for the clinical review of safety came from two placebo-controlled studies (AACG and the placebo-controlled period of AACI), a long-term extension period (AACI), an open-label study addendum (AACI Safety Addendum), and two open-label studies (AACH Part B and AACN Dona-Cohort). The table below contains the studies analyzed for the clinical review of safety.

Table 1. Studies Supporting Safety

Study	Primary Objective	Type of Study	Dose in Safety Population ^a
AACG	Evaluate the	Phase 2	Placebo (125)

Study	Primary Objective	Type of Study	Dose in Safety Population ^a
	safety and efficacy of donanemab in subjects with early symptomatic AD with presence of intermediate brain tau burden per flortaucipir PET in patients with early symptomatic AD	randomized, double-blind, placebo-controlled study	Donanemab-M: donanemab 700 mg IV infusion q 4 weeks for three doses, then 1400 mg IV infusion q 4 weeks for up to 72 weeks (131) Treatment duration: 72 weeks Follow-up: 52 weeks At Weeks 24 or 52, the donanemab dose could be reduced to 700 mg or the subject could be switched to placebo based on amyloid plaque reduction measured by florbetapir PET scan.
AACH Part B (ongoing)	Evaluate the safety, tolerability, and efficacy of donanemab in patients with early symptomatic AD	Phase 2 open-label, follow-on study for subjects who received placebo in the originating trial	Donanemab 700 mg IV infusion q 4 weeks for three doses, then 1400 mg IV infusion q 4 weeks for up to 48 weeks (55) Treatment duration: 36 or 48 weeks Follow-up: up to 24 weeks At Week 36, donanemab could be stopped based on amyloid plaque reduction measured by florbetapir PET scan.
AACI Placebo-controlled period (ongoing) ^b	Assess the safety, tolerability, and efficacy of donanemab in early symptomatic AD with the presence of brain tau pathology and to assess whether removal of existing amyloid	Placebo-controlled, randomized, double blind period of a Phase 3, multicenter study	Placebo (874) Donanemab 700 mg IV infusion q 4 weeks for three doses followed by 1400 mg IV infusion q 4 weeks (853) Treatment duration: up to 72 weeks At Weeks 24 or 52 donanemab could

Study	Primary Objective	Type of Study	Dose in Safety Population ^a
	plaque can slow progression of AD.		be switched to placebo based on amyloid plaque reduction measured by florbetapir PET scan.
AACI Long-term Extension Period (ongoing)	Further evaluate donanemab efficacy and safety over time.	Double-blind long-term extension period of a Phase 3, multicenter study	Subjects randomized to donanemab during the placebo-controlled period who did not meet dose reduction criteria would continue to receive donanemab Subjects who remained on 700 mg during the placebo-controlled period have the opportunity to dose escalate to 1400 mg Subjects who were randomized to donanemab during the placebo-controlled period who met dose-reduction criteria by Visit 21 will be assigned to receive placebo Subjects randomized to placebo during the placebo-controlled period will be assigned to receive donanemab and will follow the same dose titration as subjects in the double-blind period Donanemab (645) Treatment duration: up to 78 weeks Follow-up: up to 44 weeks At Weeks 76, 102, or 130, donanemab could be switched to placebo based on amyloid plaque reduction measured by florbetapir PET scan.
AACI Safety Addendum (ongoing)	Collect open-label exposure and safety data in patients with early	Phase 3, open-label study addendum	Donanemab 700 mg IV infusion q 4 weeks for three doses, then 1400 mg IV infusion q 4 weeks for up to 72 weeks (1047)

Study	Primary Objective	Type of Study	Dose in Safety Population ^a
	symptomatic AD who have proof of amyloid pathology and receive donanemab		Treatment duration: 72 weeks Follow-up: up to 44 weeks At Weeks 24 or 52, donanemab could be stopped based on amyloid plaque reduction measured by florbetapir PET scan.
AACN-Dona Cohort (ongoing)	To investigate amyloid plaque clearance with donanemab compared with aducanumab in patients with early symptomatic AD	Phase 3, randomized, open-label, active comparator study	Donanemab 700 mg IV infusion q 4 weeks for three doses, then 1400 mg IV infusion q 4 weeks for up to 72 weeks (71) Treatment duration: 72 weeks Follow-up: up to 44 weeks At Weeks 24 or 52, donanemab could be stopped based on amyloid plaque reduction measured by florbetapir PET scan.

AD: Alzheimer's disease, MCI: mild cognitive impairment

^aNumber of subjects at the time of the 90-Day Safety Update

^bThe Applicant considered the primary outcome of the placebo-controlled period of AACI to be complete as of April 14, 2023. At the time of the 90-Day Safety Update, four subjects were noted to be ongoing in the placebo-controlled period of AACI. The reader is referred to the [Issues Regarding Data Integrity and Submission Quality](#) section of this review for further details.

The placebo-controlled period of Study AACI was the primary source for evidence of efficacy and results from this period of the study were analyzed separately from other studies. Results from Study AACG and the placebo-controlled period of Study AACI were pooled to create a placebo-controlled pool for safety analyses. 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, which allows for analysis of adverse events occurring with exposure to donanemab for up to 12 months.

Study AACG was a randomized, double-blind, placebo-controlled study of donanemab in patients with mild cognitive impairment due to Alzheimer's disease and mild Alzheimer's dementia. The study was comprised of a 9-week screening period, an up to 72-week treatment

period with final evaluations occurring 4 weeks later at Week 76, and a 48-week follow-up period. Subjects were randomized to either donanemab 700 mg intravenously for the first three doses, then 1400 mg every four weeks for up to 72 weeks or to placebo intravenously every four weeks for up to 72 weeks.¹

In Study AACG, donanemab doses could be modified based on amyloid plaque reduction measured by florbetapir PET imaging. Depending on the degree of amyloid plaque reduction noted at Week 24 or Week 52, donanemab doses could be reduced from 1400 mg to 700 mg or the subject could be switched to placebo.

The main study of Study AACI enrolled patients with mild cognitive impairment due to Alzheimer's disease and mild Alzheimer's dementia and was comprised of a randomized, double-blind, placebo-controlled period and a double-blind long-term extension period. The study included an up to 7-week screening period, an up to 76-week double-blind period (treatment up to 72 weeks) and a 78-week extension period (treatment up to 72 weeks), and a 44-week follow-up period. In the placebo-controlled period, subjects were randomized to either donanemab 700 mg intravenously for the first three doses, then 1400 mg every four weeks for up to 72 weeks or to placebo intravenously every four weeks for up to 72 weeks. Subjects could be switched from donanemab to placebo if they met dose reduction criteria based on amyloid plaque reduction measured by florbetapir F18 PET scans. In the long-term extension period, subjects randomized to donanemab in the placebo-controlled period who had not met dose reduction criteria by Week 76 were assigned to receive donanemab. Subjects randomized to donanemab in the placebo-controlled period who had met dose reduction criteria by Week 76 were assigned placebo. Subjects randomized to placebo in the placebo-controlled period were assigned to receive donanemab in the same dose titration as subjects in the placebo-controlled period.

Study AACG differed from the other studies in that the donanemab dose could be reduced to 700 mg based on meeting amyloid plaque reduction criteria, rather than being discontinued or changed to placebo.

Subjects from Study AACD, a Phase 1b, single and multiple-dose escalation study, and 15 subjects from Study AACG who were treated with a combination of donanemab and

¹ Study AACG also included a third treatment arm: donanemab 700 mg IV infusion q 4 weeks for three doses, then 1400 mg IV infusion q 4 weeks for up to 72 weeks in combination with BACE1 inhibitor LY3202626 (n = 15 participants). The Applicant notes that this arm was discontinued after the trial began, and, as per the Applicant's prespecified analysis plan, these participants are not included in this submission (noted on page 12 of the ISAP).

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a β -site amyloid precursor protein cleaving enzyme 1 inhibitor (BACE-I) are reviewed in detail in this reviewer's Clinical Review of Safety for the initial donanemab submission, dated January 17, 2023.

Study AACC, a Phase 1 single and multiple-dose escalation study, is not included among the key studies as the maximum donanemab dose subjects received was 10 mg/kg, which was expected to result in lower exposures compared to exposures of subjects in Phase 2 and 3 studies.²

Analysis of Adverse Events

Mortality analyses were based on an on-study approach and included all deaths reported by the end of the study period (76 weeks for the placebo-controlled period of Study AACI), regardless of whether the patient discontinued from the study period.

For analyses not related to mortality, adverse events were included if they were considered treatment-emergent and occurred while the subject was on study drug or within 57 days of the last dose of the study drug (where 57 days is approximately 5-times the half-life of donanemab).

Adverse events in this review were evaluated by preferred term and by groupings of closely related preferred terms called EMQ and FMQ groupings. The reader is referred to the Appendix for a list of EMQ and FMQ groupings in this review and the preferred terms that make up the groupings.

Adverse Events of Special Interest

Amyloid related imaging abnormalities (ARIA), hypersensitivity reactions, and infusion related reactions are topics of special interest for the safety review of donanemab based on the safety profile of aducanumab and lecanemab, amyloid-directed monoclonal antibody drugs approved for the treatment of Alzheimer's disease.^{3,4}

Immunogenicity is also a topic of special interest for this review, based on the observation of infusion related reactions occurring in Phase 1 studies with donanemab.

8.2. Review of the Safety Database

² In Study AACC, donanemab was administered subcutaneously in 8 of 45 donanemab-treated participants with Alzheimer's disease.

³ Aduhelm. Labeling-Prescribing Information. Drugs@fda.gov. Action date February 8, 2023. Accessed August 25, 2023.

⁴ Leqembi. Labeling-Prescribing Information. Drugs@fda.gov. Action date July 6, 2023. Accessed August 24, 2023.

8.2.1. Overall Exposure

Overall, the Applicant met ICH guidelines of at least 300 subjects exposed to the highest clinically relevant doses that is the proposed dose for labeling (700 mg every 4 weeks for 3 doses followed by 1400 mg every 4 weeks) for six months and 100 subjects for one year. At the time of the 90-Day Safety, 1912 subjects in the all-donanemab pool were exposed to donanemab for 6 months and 1057 subjects for 12 months. The safety database includes 2899 subjects exposed to at least one dose of donanemab at any dose or route of administration, of whom 2891 received at least 1 dose intravenously. There were 2885 subjects with Alzheimer’s disease exposed to donanemab intravenously.

The dosing proposed in labeling allows for continued dosing of donanemab every 4 weeks, with decisions for continued dosing based on judgement that may be informed by amyloid imaging. This is different from dosing in the primary clinical studies for safety, AACG and AACI, in which some subjects completed a course of treatment in less than 12 months because of the dosing paradigm that either stopped or reduced dosing with donanemab once a threshold of reduction in amyloid on PET imaging was reached. Some subjects were treated longer than 12 months if they did not reach the threshold for amyloid reduction at an earlier timepoint.

The following table indicates the safety population across the clinical program at the time of the 90-Day Safety Update and includes subjects who received subcutaneous dosing in Study AACC. This reviewer notes a total of 2885 subjects with Alzheimer’s disease who received at least one dose of donanemab intravenously.⁵ Of note, subjects who received placebo in Study AACG and the placebo-controlled period of Study AACI and crossed-over to receive donanemab in follow-on Study AACH or the long-term extension period of AACI were not counted twice in the table.

Table 2. Safety Population, Size and Denominators after the 90-Day Safety Update

Safety Database for the Study Drug ^a Individuals exposed to any treatment in this development program for the indication under review N=3225 (N is the sum of all available numbers from the columns below)		
Clinical Trial Groups	Donanemab Drug (n=2899)	Placebo (n=326)
Healthy volunteers	6	0
Controlled trials conducted for this	1075	326

⁵ This includes 37 patients who received IV dosing in Study AACC, 46 patients in Study AACD, and 2,802 patients in the all-donenamb pool at the time of the 90-Day Safety Update.

indication ^b		
All other trials conducted for this indication ^c	1818	n/a

^a Study drug means the drug being considered for approval.

^b Includes 8 subjects from Study AACC who were dosed subcutaneously with donanemab. Fifteen subjects from Study AACC who received a combination of donanemab and a β -site amyloid precursor protein cleaving enzyme 1 inhibitor (BACE-I) were not included.

^c To avoid double-counting subjects, 55 subjects who received placebo in Study AACC and 645 subjects who received placebo in Study AACI placebo-controlled period and then switched to donanemab in the follow-on Study AACH and Period AACI LTE, respectively, were not included in the total for placebo.

The Applicant met ICH guidelines of at least 300 subjects exposed to the highest clinically relevant doses (700 mg every 4 weeks for 3 doses followed by 1400 mg every 4 weeks) for six months and 100 subjects for one year.

Duration of exposure to study drug was calculated based on the proposed dosing of donanemab, which is 700 mg every four weeks for the first three doses, followed by 1400 mg every four weeks.

At the time of the 90-Day Safety Update, the Division calculated 1912 subjects with at least 6 months of exposure, 1057 subjects with at least 12 months of exposure, and 432 subjects with at least 18 months of exposure in the all-donanemab pool. The following table shows the Division's calculations for subjects with 6-month and 12-month exposures in the placebo-controlled and all-donanemab pool at the 90-Day Safety Update.

Table 3. Duration of Exposure Based on Donanemab Infusions in the Placebo-Controlled Pool, Study AACI, and the All-Donanemab Pool after the 90-Day Safety Update.^a

	All PC	AACI	All Dona
Exposure time	(N = 984)	(N = 853)	(N = 2802)
>= 6 months	783 (79.6%)	690 (80.9%)	1912 (68.2%)
>= 12 months	524 (53.3%)	486 (57.0%)	1057 (37.7%)
>= 18 months	230 (23.4%)	215 (25.2%)	432 (15.4%)
>= 26 months	0	0	28 (1.0%)
>= 33 months	0	0	0

^aUp to three doses of < 1400 mg doses were counted as a month of exposure for each subject, to account for the proposed titration dose of 700 mg for the first three doses. All 1400 mg infusions were counted as a month of exposure.

The Division's method for calculating exposure differed slightly from the Applicant's method (see [Appendix](#) for further details).

The overall number of subjects (healthy and those with Alzheimer's disease) who received at

least one intravenous dose of donanemab (partial or complete infusion) across the clinical program at the time of the 90-Day Safety Update was 2891.⁶

The primary safety data are from Study AACG and the placebo-controlled period of Study AACI. The dosing regimen in AACG provided for 700 mg q 4 weeks for 3 doses followed by 1400 mg q 4 weeks for up to 72 weeks, with an allowance for reduction to 700 mg or placebo based on amyloid plaque reduction at weeks 24 or 52 or based on the development of ARIA-E. The dosing regimen in AACI provided for 700 mg q 4 weeks for 3 doses followed by 1400 mg q 4 weeks for up to 72 weeks, with an allowance for reduction to placebo based on amyloid plaque reduction at weeks 24 or 52.⁷ Ongoing open-label extension period AACI and open-label studies AACH Part B, AACI Safety Addendum, and AACN-Dona Cohort, with the same titration and that also include an allowance for stopping treatment based on amyloid plaque or development of ARIA-E, provide supportive information and were pooled with donanemab-treated subjects from Studies AACG and the placebo-controlled period of Study AACI to create an all-donanemab pool allowing for analysis of adverse events occurring in subjects who have had exposure for up to 12 months.

Reviewer comment: As noted above, the proposed treatment regimen is different from donanemab dosing in AACG and AACI, in that donanemab was discontinued after achieving amyloid plaque reduction criteria in the clinical studies, whereas the regimen in the proposed labeling allows for clinical judgement to be used when considering continuing or stopping treatment in the absence of a safety issue.

The following table shows the number of subjects from Studies AACG and the placebo-controlled period of Study AACI in the placebo-controlled pool.

Table 4. Number of Subjects from Studies AACG and AACI in the Placebo-Controlled Pool

Study	Donanemab N=984	Placebo N=999
AACG	131	125
AACI	853	874

The above table was created by this reviewer.

The cutoff dates for the 90-Day Safety Update was June 7, 2023, for the ongoing placebo-

⁶ This includes 2802 participants in the all-donanemab pool as well as 46 participants from Study AACD and 43 participants from Study AACG (6 health volunteers and 37 patients). It does not include 8 subjects from AACG who were dosed subcutaneously with donanemab.

⁷ The protocol for AACI was amended to add a titration period of 700 mg for the first three doses prior to starting the 1400 mg dose. Approximately 5% of participants received 1400 mg as the initial dose (43/853) per CSR for AACI (page 98).

controlled and long-term extension periods of AACI, AACI Safety Addendum, AACH, and AACN.⁸

At the time of the 90-Day Safety Update, the all-donanemab pool contained 2802 subjects.

The following table shows the number of subjects from each of the studies that contributed to the all-donanemab pool at the time of the 90-Day Safety Update.

Table 5. Number of Subjects from the Studies that Contribute to the All-Donanemab Pool at the 90-Day Safety Update

Study	Donanemab N=2802
AACG	131
AACH Part B	55
AACI Main (PC + LTE)	1498
AACI Safety Addendum	1047
AACN-Dona Cohort	71

PC: placebo-controlled period. LTE: long-term extension period

The above table was created by this reviewer.

In AACI, approximately 12-13% ([103-114]/853) had switched to placebo by weeks 28 through 52, and approximately 31-33% ([265-281]/853) had switched to placebo by weeks 56-72. This switch could complicate interpretation of overall findings of adverse reactions in donanemab treated subjects compared to placebo; subjects were analyzed according to their randomization to donanemab or placebo. The following figure shows the distribution of donanemab doses over time in subjects in Study AACI (placebo-controlled period + long-term extension period). For a distribution of donanemab doses over time in Study AACG, the reader is referred to this reviewer's review dated January 18, 2023, for the initial donanemab submission.

⁸ Cutoff date for the placebo-controlled period of AACI indicated in the Applicant's response dated October 19, 2023, to an information request dated October 19, 2023.

Figure 1. Donanemab-Dose Distribution Over Time in Study AACI.

TIME (weeks)	0 mg	700 mg	1400 mg
0	0	95% (810/853)	5% (43/853) ^a
4	0	96% (792/821) ^b	3% (28/821)
8	0	98% (751/765)	2% (14/765)
12	0	9% (63/678)	91% (615/678)
16	0	5% (36/678)	95% (642/678)
20	0	7% (52/697)	93% (645/697)
24	0	7% (48/643)	93% (595/643)
28	16% (103/638)	6% (37/638)	78% (498/638)
32	17% (112/641)	5% (35/641)	77% (494/641)
36	17% (110/638)	5% (31/638)	78% (497/638)
40	18% (112/637)	4% (27/637)	78% (498/637)
44	18% (114/645)	4% (24/645)	79% (507/645)
48	18% (113/639)	4% (24/639)	79% (502/639)
52	19% (110/591)	2% (14/591)	79% (467/591)
56	46% (265/571)	2% (12/571)	51% (294/571)
60	48% (273/569)	2% (12/569)	50% (284/569)
64	48% (274/569)	3% (15/569)	49% (280/569)
68	49% (280/570)	3% (15/570)	48% (275/570)
72	49% (281/572)	2% (13/572)	49% (278/572)
78 ^c	69% (333/483)	2% (8/483)	29% (142/483)

Abbreviations: AACI-PC = Study AACI placebo-controlled; PET = positron emission tomography.

- ^a Amendment (a) of the protocol introduced a titration period of 700 mg for the first 3 doses. Some participants were enrolled prior to the amendment and started dosing on 1400 mg.
- ^b One participant (1/821) at Week 4 had 1050 mg dispensed from the pharmacy, but 700 mg was actually dosed.
- ^c Week 78 reflects the first dosing period in the long-term extension after the final PET scan of the AACI-PC period.

The above figure is composed of two screenshots from the Applicant's response dated August 23, 2023, to an information request dated August 17, 2023. The denominator for each week is the total number of subjects with a dosing event. Denominators increase and decrease based on subjects stopping or holding infusions or restarting.⁹

8.2.2. Relevant characteristics of the safety population:

Similar to the initial donanemab submission, a lower incidence of female subjects, subjects of a minority race and ethnicity, and age over 85 years were observed in the placebo-controlled pool compared to expected incidences in the U.S. population with Alzheimer's disease. The safety profile of donanemab in subjects with more advanced stages of AD is unknown as the

⁹ Noted in the Applicant's response dated January 12, 2024, to an information request dated January 10, 2024.

population enrolled in AACG and AACI was identified as having mild cognitive impairment (MCI) or mild AD.

Baseline demographics were similar between the donanemab and placebo arms in the placebo-controlled period of Study AACI. Similar findings were observed for the pooled placebo-controlled studies in that donanemab and placebo arms had similar baseline demographics.

The following table shows baseline demographics for the placebo-controlled period of AACI. The reader is referred to the [Appendix](#) for baseline demographics for the placebo-controlled pool.

Table 6. Baseline Demographics for the Placebo-Controlled Period of Study AACI

Characteristic	Donanemab (N = 853)	Placebo (N = 874)
Sex, n (%)		
Male	365 (42.8)	373 (42.7)
Female	488 (57.2)	501 (57.3)
Age, years		
N	853	874
Mean (SD)	72.93(6.149)	73.06(6.192)
Median (Min, Max)	73.00(59.0, 86.0)	74.00(59.0, 85.0)
Age groups (years), n (%)		
<65	88 (10.3)	86 (9.8)
65 - <75	414 (48.5)	402 (46.0)
75 - <85	336 (39.4)	373 (42.7)
>= 85	15 (1.8)	13 (1.5)
Race, n (%)		
AMERICAN INDIAN OR ALASKA NATIVE	2 (0.2)	0 (0.0)
ASIAN	57 (6.7)	47 (5.4)
BLACK OR AFRICAN AMERICAN	19 (2.2)	20 (2.3)
MULTIPLE	0 (0.0)	1 (0.1)
WHITE	774 (90.7)	806 (92.2)
Ethnicity, n (%)		
HISPANIC OR LATINO	35 (4.1)	37 (4.2)
NOT HISPANIC OR LATINO	806 (94.5)	823 (94.2)
NOT REPORTED	12 (1.4)	14 (1.6)
Region, n (%)		
Australia	13 (1.5)	4 (0.5)
Europe	115 (13.5)	124 (14.2)
Japan	45 (5.3)	43 (4.9)
North American (US and Canada)	680 (79.7)	703 (80.4)
BMI (kg/m2)		
N	853	874

Characteristic	Donanemab (N = 853)	Placebo (N = 874)
Mean (SD)	25.98(4.831)	25.70(4.748)
Median (Min, Max)	25.51(13.0, 47.4)	25.18(15.9, 49.4)
BMI Tertiles		
<23.36	268 (31.4)	302 (34.6)
23.36 - < 27.50	296 (34.7)	290 (33.2)
>= 27.50	289 (33.9)	282 (32.3)
Microhemorrhage Presence on Baseline Screening MRI	41 (4.8)	38 (4.3)
Not on Antithrombotic	504 (59.1%)	513 (58.7%)
On Antithrombotic	349 (40.9%)	361 (41.3%)
Aspirin <= 81 mg alone	206 (24.2%)	222 (25.4%)
Aspirin > 81 mg, other antiplatelet or combination of aspirin and other antiplatelet	60 (7.0%)	53 (6.1%)
Anticoagulation (alone or combined with other antithrombotic)	83 (9.7%)	86 (9.8%)
ApoE ε4		
Unknown	3 (0.4)	4 (0.5)
Non-carrier	255 (29.9)	250 (28.6)
Heterozygote	452 (53.0)	474 (54.2)
Homozygote	143 (16.8)	146 (16.7)
Disease Severity Status		
MCI (MMSE>26)	145 (17.0)	138 (15.8)
Mild (20<=MMSE<=26)	707 (82.9)	736 (84.2)
Moderate (MMSE<20)	1 (0.1)	0 (0.0)

BMI: Body mass index. MCI: mild cognitive impairment. MMSE: Mini-Mental Status Examination. This table was created by Senior Clinical Analyst Dr. Rui Li.

For labeling purposes, 90% (765/853) of donanemab-treated subjects in the placebo-controlled period of AACI were age 65 years and older, and 41% (351/853) were age 75 years and older.

Subjects in the donanemab and placebo arms also had similar baseline measures of cognitive function, diagnosis duration, years of education, and use of acetylcholinesterase inhibitors or memantine at baseline in the placebo-controlled period of Study AACI and the pooled placebo-controlled studies.

Reviewer comment:

The population studied was healthier than the general population with Alzheimer's disease. The population enrolled in AACG and AACI were identified as having mild cognitive impairment (MCI) or mild AD. In Study AACI, subjects were excluded if they had significant neurological disease affecting the central nervous system other than AD, serious or unstable illness that could interfere in analysis of the study (according to the investigator's opinion), life expectancy of < 24

months, history of cancer within the past 5 years, except for cancers with low risk of recurrence or spread, or had a psychiatric diagnosis that could confound the interpretation of drug effect (in the investigator's opinion). Study AACG had similar exclusion criteria.

A slightly lower proportion of females was observed in the safety population of the pooled placebo-controlled studies compared to the proportion of women with AD reported in the Alzheimer's Association 2023 report. According to the Alzheimer's Association 2023 Alzheimer's Disease and Facts and Figures, which contains U.S. data related to Alzheimer's disease, approximately two-thirds of Americans with Alzheimer's are women.¹⁰

For subjects 65 years and older, a lower proportion of subjects 75 years to 84 years of age and 85 years of age and older was observed in the pooled placebo-controlled studies compared to the population noted in the Alzheimer's Association 2023 report. In this report, in a population-based study of chronic health conditions of older people in the United States, the percentage of people with Alzheimer's dementia increased with age: 5% in ages of 65 to 74 years, 13% in ages 75 to 84 years, and 33% in ages 85 years and older.

African Americans and Hispanics were underrepresented in the pooled placebo-controlled studies compared to the general United States population,¹¹ although at increased risk for Alzheimer's disease as noted in the Alzheimer's Association 2023 report.¹² In this report, studies on race and ethnicity in older populations demonstrate that compared to Whites, African Americans are twice as likely to have Alzheimer's dementia, and Hispanics are about 1.5 times as likely.

The proportion of the population studied with at least one allele for ApoE ϵ 4 was representative of the population with AD noted in the Alzheimer's Association 2023 report.¹³ In this report, approximately two-thirds of people living in the United States have at least one copy of the ApoE ϵ 4 gene.

Patients were excluded by protocol from Study AACI, AACG, and AACN-Dona Cohort if they had a baseline MRI that demonstrated presence of ARIA-E, > 4 cerebral microhemorrhages, more than 1 area of superficial siderosis, any macrohemorrhage or severe white matter disease.

Reviewer comment: The safety profile of donanemab in subjects with more advanced stages of Alzheimer's dementia is unknown as subjects enrolled in AACG and AACI were identified as

¹⁰ Alzheimer's Association. 2023 Alzheimer's disease facts and figures. *Alzheimers Dement* 2023; 19: 1598-1695. doi: 10.1002/alz.13016

¹¹ <https://www.census.gov/quickfacts/fact/table/US/PST045223>

¹² <https://www.alz.org/media/Documents/alzheimers-facts-and-figures.pdf>

¹³ <https://www.alz.org/media/Documents/alzheimers-facts-and-figures.pdf>

having MCI or mild AD. Additionally, subjects with other serious or unstable illnesses that could potentially impact interpretation of the results of drug effect were not included in the studies, and safety outcomes from these studies may underestimate the impact of adverse events in this population.

In Studies AACG and AACI, subjects were allowed to use approved medications for Alzheimer's disease concomitantly and there were no exclusion criteria related to antithrombotics use.

Because subjects with no or very low tau burden as assessed by PET were excluded from AACG and the main study of AACI, the incidence of adverse events in the no/very low tau burden population was a topic of special interest for this review. Subjects with no or very low tau burden were enrolled in AACI Safety Addendum. The reader is referred to the section of [Adverse Events in No/Very Low Tau Burden Population](#) for further details related to the safety profile of donanemab in a population of subjects with no or very low tau burden as assessed by PET.

Baseline characteristics for the all-donanemab pool were similar to the placebo-controlled pool.

8.2.3. Adequacy of the safety database:

The exposure of the safety database overall appears adequate in terms of size and dosing. Exposure in the all-donanemab pool meet ICH E1A guidelines for exposure of at least 300 subjects at 6 months and 100 subjects at 12 months at the proposed dose. The clinical program met ICH E1A guidelines for having at least 1500 subjects exposed to study drug overall as the number of subjects exposed to at least one dose of donanemab was 2,891. Minority groups, including Blacks and Hispanics or Latinos, were underrepresented. The safety database consisted primarily of subjects with mild cognitive impairment and mild Alzheimer's disease, which is the proposed target population.

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

Quality issues in the submission have been addressed by the Applicant, subsequent to information requests (see the [Appendix](#) for details).

Overall, the submission was well-organized.

8.3.2. Categorization of Adverse Events

This reviewer notes that the method of recording AEs of ARIA-H in the adverse event datasets likely underrepresent the incidence of ARIA-H experienced by subjects in Studies AACG, AACH,

and AACI, and that data from MRIs likely provides a better approximation of the incidence of ARIA-H. This reviewer considered the definitions for TEAEs and SAEs to be acceptable. Translation of verbatim terms for adverse events to MedDRA preferred terms was adequate, except as noted below for four subjects including one subject with an adverse event of intracerebral hemorrhage.

As noted in this reviewer's Safety Review dated January 17, 2023, ARIA events were recorded as adverse events and as MRI findings in AACG and AACI. ARIA-E findings were required to be reported as adverse events by investigators, but this was not specified for ARIA-H events. This reviewer considered the dataset containing MRI findings to be the more comprehensive dataset for ARIA findings and as a result, analyses related to ARIA and intracerebral hemorrhage use the MRI dataset unless otherwise specified.

Analyses of adverse events for this review used the integrated database.

In the ISS, the Applicant's analyses of adverse events of the pooled placebo-controlled studies and the all-donanemab pool used the integrated database, whereas the Applicant's analyses of adverse events occurring in Study AACI used the AACI database. Differences in the Applicant's definition of baseline in the integrated database compared to Study AACI database resulted in differences in the numbers of adverse events considered treatment-emergent. In Study AACI adverse events were considered baseline if they occurred *prior to* the informed consent date in contrast to the IDB where adverse events were considered baseline if they occurred *up to* the informed consent date.¹⁴

Adverse events in the integrated database were coded to Medical Dictionary for Regulatory Activities (MedDRA) version 25.1.

The protocol for Study AACI specified that all adverse events occurring after signing of the informed consent form were to be recorded in the case report form. Adverse events were collected at every visit, which occurred every four weeks during the placebo-controlled and long-term extension periods, and then quarterly during the follow-up period (starting 12 weeks after the last dose of investigational product). The protocol specified that for adverse events that were serious or were AEs of special interest, the subject should be followed until the event resolves, stabilizes, or is reasonably explained or the subject was lost to follow-up. Treatment-emergent adverse events (TEAEs) were defined as untoward medical occurrence that emerged during a defined treatment period, having been absent pretreatment (prior to the informed consent date), or worsens relative to the pretreatment state, and does not necessarily have a causal relationship with the treatment. A serious adverse event (SAE) was defined as any AE that result in death, initial or prolonged inpatient hospitalization, was life-threatening,

¹⁴ Noted in the Applicant's response dated July 24, 2023, to an information request dated July 21, 2023.

persistent disability/incapacity, congenital anomaly/birth defect, or an important medical event that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the outcomes listed above. Adverse events were coded to Medical Dictionary for Regulatory Activities (MedDRA) version 25.1.

This reviewer noted the following adverse events were incorrectly coded from the verbatim to their preferred terms in Study AACI. In a response dated July 31, 2023, the Applicant submitted updated adverse event datasets and analyses that were affected by the updated preferred terms.

Table 7. Updated Adverse Event Terms

USUBJID	Reported Term	Applicant's MedDRA Preferred Term	Division's MedDRA Preferred Term
I5T-MC-AACI- (b) (6)	1-2 mm left sided calyceal calculi	Renal cyst	Nephrolithiasis
I5T-MC-AACI- (b) (6)	ECCHYMOSIS BRIDGE OF NOSE	Epistaxis	Ecchymosis
I5T-MC-AACI- (b) (6)	0/4 deep tendon reflex patella bilaterally	Hyperreflexia	Hyporeflexia
I5T-MC-AACI- (b) (6)	Macrohemorrhage (ARIA-H Left Occipital)	Amyloid related imaging abnormality- microhemorrhages and hemosiderin deposits	Intracerebral hemorrhage

For studies AACG, AACI Safety Addendum, AACH Part B, and AACN-Dona Cohort, this reviewer considered the definitions for TEAEs and SAEs to be acceptable. In Study AACG, severity of AEs was based on the judgement of the principal investigator rather than on defined categories and could potentially result in inconsistent AE severity categorization among different principal investigators. Differences in the Applicant's definition of baseline adverse events in Study AACH compared to the integrated database (IDB) resulted in differences in the numbers of adverse events considered treatment-emergent. In Study AACH, an adverse event was considered a baseline event regardless of whether it had ended before the first dose in contrast to the IDB where adverse events were considered baseline events if they were ongoing at the time of the first dose.¹⁵ The reader is referred to this reviewer's Safety Review dated January 17, 2023, for further details on categorization of adverse events in Study AACG, AACI Safety Addendum, AACH Part B, and AACN-Dona Cohort.

¹⁵ Noted in the Applicant's response dated July 24, 2023, to an information request dated July 21, 2023.

8.3.3. Routine Clinical Tests

Overall, this reviewer found the safety assessment methods and timepoints to be adequate for the safety review. In the placebo-controlled and long-term extension periods of Study AACI, safety assessments included regular monitoring and recording of vital signs, including blood pressure, pulse, and temperature, regular monitoring of hematology, chemistry, and urine analysis tests, and ECGs. Details are provided in the [Appendix](#).

For the schedule for MRIs for assessments related to ARIA, the reader is referred to Section 8.5.1 ARIA of this review.

8.4. Safety Results

8.4.1. Deaths

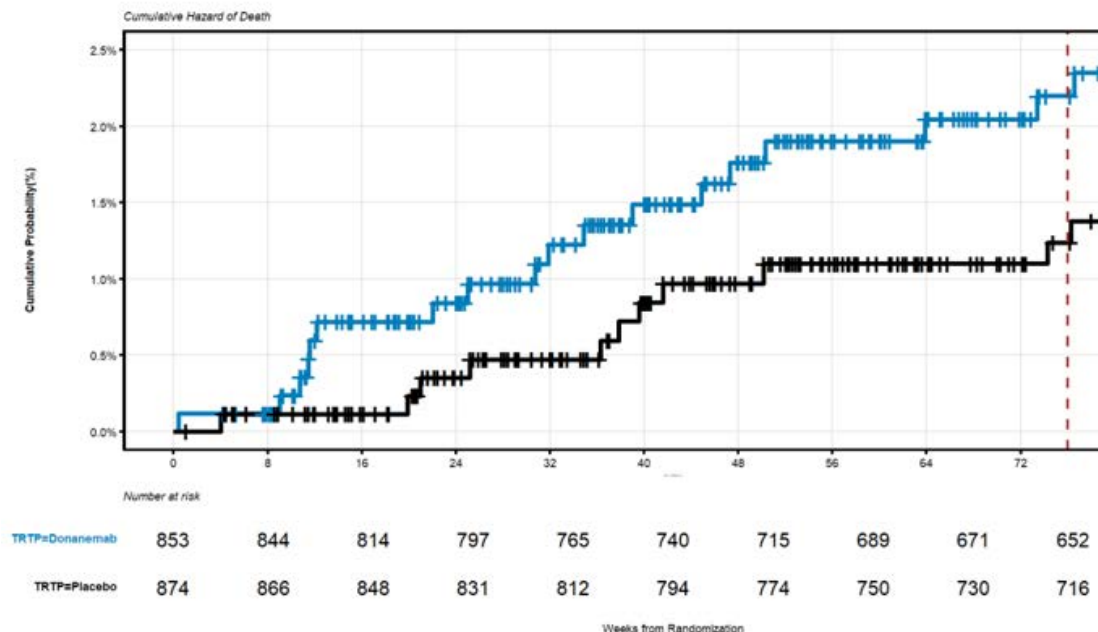
In the placebo-controlled period of AACI, using an on study approach for evaluation, mortality at 76 weeks occurred in 2.2% (17/853) of subjects randomized to donanemab and in 1.2% (10/874) of subjects randomized to placebo, risk difference (95% CI) 1.0% (-0.3%, 2.3%), hazard ratio (95% CI) 1.80 (0.83, 3.94).¹⁶ Taking into consideration three amyloid related imaging abnormalities-related deaths, which occurred in donanemab-treated patients, the non-ARIA related mortality at 76 weeks occurred in 1.8% (14/853) of subjects randomized to donanemab and in 1.2% (10/874) of subjects randomized to placebo, risk difference (95% CI) 0.6% (-0.6%, 1.8%), hazard ratio (95% CI) 1.49 (0.66, 3.35).¹⁷ Data from participants who continued into the LTE or were newly started on donanemab from placebo in the Safety Addendum were included in the All-Donanemab pool. In the all-donanemab pool, the deaths occurred in 1.3% (37/2802).¹⁸

¹⁶ Li, P, Zhao F, Zhao Y, Soukup M. Statistical Memo dated March 4, 2024, and Statistical Memo Addendum dated April 26, 2024, where mortality incidences are Kaplan-Meier estimates of cumulative incidence.

¹⁷ DBVII Statistical Reviewer's analysis using SUBJINFO.XPT in SN161, where mortality incidences are Kaplan-Meier estimates of cumulative incidence.

¹⁸ Crude percentage

Figure 2. Kaplan-Meier Cumulative Probability for Death, Study AACI, 76 Weeks



Source: Statistical reviewer's memo dated April 26, 2024 using SUBJINFO.XPT in SDN161.

In the placebo-controlled period of Study AACI, approximately 26% of donanemab-treated patients withdrew from the study compared to 20% on placebo. After withdrawing from the study, vital status at Week 76 was not captured for these patients by the Applicant.

Reviewer comment: The lack of vital status information collected during the conduct of Study AACI added uncertainty to the mortality analysis, for which there was an imbalance in deaths observed with donanemab relative to placebo.

With high rates of missing vital status data at Week 76 and its potential impact on the assessment of mortality, the Division requested that the Applicant retrieve additional mortality information among patients who discontinued Study AACI prior to Week 76 and for whom the vital status was not available at the time of the 90-Day safety update. Using a third-party vendor, the applicant retrieved vital status through publicly available records and databases, social media, and traditional media. Information on cause of death is still not available. Among 352 participants (198 for donanemab and 154 for placebo) whose vital status was unknown, the vital status of 52% (184 participants) was retrieved: 118 for donanemab and 66 for placebo, respectively. Among the participants with retrieved vital status information, two participants randomized to donanemab died within 76 weeks and six participants randomized to placebo died within 76 weeks.

Incorporating these retrieved deaths into the deaths observed during the trial resulted in 19 deaths on donanemab and 16 deaths on placebo.

Limitations of these data include that the additional death information was obtained through a different approach from the approach planned in Study AACI, and included publicly available information in records, databases, social media, and traditional media. Additionally, approximately 10% of patients still had missing vital status information and the retrieved vital status information lacked information on the cause of death.

Table 8. Updated Mortality Assessment of the Placebo-Controlled Period of AACI; On Study Approach

	Donanemab N=853 n (% ^a)	Placebo N=874 n (% ^a)
Mortality at 76 weeks	19 (2.3%)	16 (1.9%)

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

^aKaplan-Meier estimates of cumulative incidence.

As deaths are not uncommon in the population of older adults typically enrolled in AD trials, it is useful to consider the imbalance of deaths observed in AACI with mortality findings from other recent placebo-controlled clinical trials of amyloid-targeting monoclonal antibodies, which are shown in the table below. The studies were comparable in terms of age of the subjects and ApoE ε4 genotype. Clinical trials with donanemab compared to other monoclonal antibodies included a population with more advanced disease (higher proportion of subjects with mild AD compared to mild cognitive impairment, with 82% of subjects in the placebo-controlled pool for donanemab having mild AD at baseline compared to 38% in pooled trials for lecanemab and 45% in pooled trials for gantenerumab)].^{20,21} Overall, there is not a signal for mortality in other drugs in the class of amyloid-targeting monoclonal antibodies.

When comparing AACI to individual studies, it is important to consider the time period when the studies were conducted as the COVID pandemic has been shown to impact mortality rates in clinical trials broadly. For donanemab, AACG took place from 2017-2020 and AACI took place from 2020-2023. Of the trials listed, the gantenerumab trials were conducted in a time period

¹⁹ Updated mortality information noted in responses submitted by the Applicant April 24 2024, and May 14, 2024.

²⁰ Bateman R, Smith J, Donohue M, et al. Two Phase 3 Trials of Gantenerumab in Early Alzheimer’s Disease. N Engl J Med 2023; 389:1862-1876.

²¹ Erten-Lyons, D. Clinical Review of Lecanemab BLA 761269; July 5, 2023, and January 5, 2023

most comparable to that of donanemab, encompassing the period during which COVID 19 surfaced. The two gantenerumab show variability in the mortality rates across the two studies with an imbalance favoring drug in one study and an imbalance favoring placebo in the other study. The comparison of incidence of death in the donanemab program to the aducanumab program is limited by early termination of the aducanumab Phase 3 studies. Overall, the comparison to other AD trials shows that mortality rates can vary across studies, and that the mortality rates in AACI in the placebo arm are within the background rate of deaths reported in placebo arms across multiple studies.

Table 9. Fatal Events Across Placebo-Controlled Trials of Amyloid-Targeting Monoclonal Antibodies

Study	Dates of placebo-controlled period	Drug % (n/N)	Placebo % (n/N)
Donanemab AACG	2017-2020	0.8% (1/131)	0.8% (1/125)
Donanemab AACI	2020-2023	2.0% (17/853)	1.1% (10/874)
Gantenerumab/Graduate I ^a	2018-2023	0.6% (3/503)	2.1% (10/481)
Gantenerumab/Graduate II ^a	2018-2023	1.4% (7/501)	0.8% (4/474)
Lecanemab 201 ^b	2012-2018	0.8% (5/609)	0.8% (2/245)
Lecanemab 301 ^c	2019-2021	0.7% (6/898)	0.8% (7/897)
Aducanumab 301 ^d	2015-2019	0.5% (5/1107)	0% (0/540)
Aducanumab 302 ^d	2015-2019	0.5% (6/1091)	0.9% (5/547)

^aTable 3. Bateman RJ, Smith J, Donohue MC, et al. Two Phase 3 Trials of Gantenerumab in Early Alzheimer's Disease. N Engl J Med 2023; 389:1862-76.

^bClinical Review of Lecanemab BLA 761269; January 5, 2023.

^cTable 3. Van Dyck CH, Swanson CJ, Aisen RJ, et al. Lecanemab in Early Alzheimer's Disease. N Engl J Med 2023; 388:9-21.

^dClinical Review of Aducanumab BLA 761178; June 6, 2021. These studies were terminated early.

The mortality rate observed in donanemab-treated subjects in the placebo-controlled period of AACI or the all-donanemab pool did not exceed the mortality rate observed in a U.S. population of community-dwelling people with Alzheimer's disease; however, the clinical trial population was likely healthier than the community-dwelling population with AD based on population inclusion and exclusion criteria. Based on the 90-Day Safety Update database cutoff date of June 7, 2023, incidence of death by person-years of exposure to donanemab in the placebo-controlled period of AACI is 15.0/1,000 person-years (17/1137.0 person-years) and in the all-

donanemab pool is 15.9/1,000 person-years (37/2322 person-years).²² In a 15-year prospective cohort study of subjects age > 65 years or older, the mortality rate in subjects with Alzheimer’s disease (unadjusted for age or sex) was observed to be 133.8/1,000 person-years²³, and was higher than that observed in the placebo-controlled period of AACI or the all-donanemab pool. The populations in the placebo-controlled period of AACI and the all-donanemab pool were likely healthier than the cohort population studied given that patients were excluded if they had a more advanced stage of AD, serious or unstable illnesses, other significant neurological disease affecting the central nervous system other than Alzheimer’s disease, or a life expectancy of < 24 months, among other criteria.

ARIA-related deaths in occurred in 0.4% (3/853) of donanemab-treated subjects in AACI compared to none in placebo. In one of these subjects, intracerebral hemorrhage occurred with ARIA-E and ARIA-H in the setting of findings that can be seen with cerebral amyloid angiopathy (see table below). In the all-donanemab pool, there was an additional death associated with ARIA and an additional death associated with intracerebral hemorrhage that occurred in a subject with ARIA-E, with symptoms mimicking stroke who was treated with thrombolytic therapy. There was no other unusual cluster of deaths in the database.

The following table shows incidence of adverse events with fatal outcome by preferred term and grouped by system organ classes (SOC) in the placebo-controlled period of AACI at Week 76.

Table 10. Incidence of Adverse Events with Fatal Outcome in the Placebo-Controlled Period of AACI at Week 76^a

Preferred Term	Donanemab N=853 n (%)	Placebo N=874 n (%)
Subjects with Adverse Events with Fatal Outcome	17 (2.0)	10 (1.1)
Nervous system disorders	5 (0.6)	1 (0.1)
Amyloid related imaging abnormality-edema/effusion (ARIA-E) ^b	1 (0.1)	0
(ARIA-E) and Amyloid related imaging abnormality-microhemorrhages and hemosiderin deposits (ARIA-H) ^c	1 (0.1)	0
Intracerebral hemorrhage ^d	1 (0.1)	0
Subarachnoid hemorrhage	1 (0.1)	0

²² Average person-years of exposure in the placebo-controlled period of AACI is noted in an email from Statistician Dr. Fengyu Zhao dated April 12, 2024. Person-years of exposure for the all-donanemab pool is noted in the response dated January 18, 2024, to an information request dated January 17, 2024.

²³ Ganguli M, Dodge HH, Shen C, Pandav RS, DeKosky ST. Alzheimer Disease and Mortality. Arch Neurol 2005; 779-784.

Preferred Term	Donanemab N=853 n (%)	Placebo N=874 n (%)
Dementia Alzheimer's type	1 (0.1)	1 (0.1)
General disorders and administration site conditions	1 (0.1)	1 (0.1)
Death	1 (0.1)	1 (0.1)
Infections and infestations	3 (0.4)	4 (0.5)
COVID-19	1 (0.1)	0
COVID-19 pneumonia ^e	1 (0.1)	1 (0.1)
Pneumonia	1 (0.1)	2 (0.2)
Sepsis	0	1 (0.1)
Gastrointestinal disorders	1 (0.1)	0
Retroperitoneal hemorrhage	1 (0.1)	0
Metabolism and nutrition disorders	1 (0.1)	0
Dehydration	1 (0.1)	0
Psychiatric disorders	2 (0.2)	1 (0.1)
Completed suicide	2 (0.2)	1 (0.1)
Respiratory, thoracic and mediastinal disorders	4 (0.5)	0
Pulmonary embolism	2 (0.2)	0
Respiratory arrest	1 (0.1)	0
Respiratory failure	1 (0.1)	0
Injury, poisoning and procedural complications	0	1 (0.1)
Respiratory fume inhalation disorder	0	1 (0.1)
Vascular disorders	0	1 (0.1)
Arteriosclerosis	0	1 (0.1)
Cardiac disorders	0	1 (0.1)
Myocardial infarction	0	1 (0.1)

The reviewer created this table using the 90DaySafety Update IDB ADAE dataset, DTHAEFL = Yes, STUDYID = AACI, APERIODC = First treatment period or missing, AEENDY = ≤ 532 and USUBJID from ADSL not equal to AACIA9FL = Y and ISAFFL = Y.

^aPercentages are based on crude percentages.

^bI5T-MC-AACI- (b) (6)

^cSubject I5T-MC-AACI- (b) (6) the preferred term was “death.” The events associated with death were ARIA-E and ARIA-H.

^dI5T-MC-AACI- (b) (6) intracerebral hemorrhage in the setting of ARIA-H and ARIA-E, with superficial siderosis at baseline

^eThis includes I5T-MC-AACI- (b) (6) with respiratory failure in the setting of COVID-19 pneumonia

Deaths in subjects on donanemab in the placebo-controlled pool, including those beyond 76 weeks, are briefly described in the following table.

Table 11. Deaths in Donanemab-Treated Subjects in the Placebo-controlled Pool, Including Beyond 76 Weeks

Subject ID	Age/Sex	Study Day Onset	Brief Narrative (Fatal AE term in bold)
15T-MC-AACI- (b) (6)	72F	66	Presented with confusion, agitation, forgetfulness, short attention span, garbled speech, and disorientation, and reporting the SAE of ARIA-E (severe); placed on hospice Received 3 doses of donanemab; last dose on Study Day 56 PMH: ApoE ε3/ε4, chronic renal failure
15T-MC-AACI- (b) (6)	75M	413	Reported to experience confusional state (moderate) and balance disorder (moderate) and found to have severe ARIA-E. Admitted to ED on Study Day 427 with nausea and vomiting with severe ARIA-E/H Received 10 doses of donanemab; last dose on Study Day 399 PMH: ApoE ε4 heterozygote, chronic kidney disease stage 3, hypertension, hyperlipidemia, type 2 diabetes mellitus, aortic arteriosclerosis, balance disorder
15T-MC-AACI- (b) (6)	72M	72	Developed right hemiplegia and aphasia on Study Day 72 and was diagnosed with severe intracerebral hemorrhage and hemorrhagic stroke with mass effect; Received aspirin of unknown quantity at onset of symptoms MRI on day prior to the event showed mild ARIA-E/ARIA-H (microhemorrhage and superficial siderosis) 2 doses; last dose of donanemab on Study Day 29 PMH: ApoE ε3/ε3genotype, with bowel cancer, history of brain trauma, migraines, hypertension, hypercholesterolemia
15T-MC-AACI- (b) (6)	84M	237	Developed subarachnoid hemorrhage after fall from a ladder 6 doses of donanemab; last dose day 162

Subject ID	Age/Sex	Study Day Onset	Brief Narrative (Fatal AE term in bold)
			PMH of falls, unsteadiness; and concomitant acetylsalicylic acid use
15T-MC-AACI- (b) (6) (b) (6)	82M	70	COVID-19 pneumonia reported on Day 70. On Study Day 85, the subject become hypoxic, bradycardic, and then died. The cause of death was reported as complications of Covid-19. An autopsy was not performed. 3 doses; last dose on Day 55. PMH of chronic bronchitis, asthma, and COPD, DM2 with nephropathy, unvaccinated status for Covid-19 were likely contributory factors. Also with PMH of mild dementia.
15T-MC-AACI- (b) (6) (b) (6)	79M	346	The subject presented to the ER unresponsive and was found to have a UTI and Covid-19 pneumonia. Death on day 352. He had received two doses of Covid vaccine approximately a year before. 13 doses; last dose on Day 337. PMH of COPD, dementia
15T-MC-AACI- (b) (6) (b) (6)	68M	78	Delirium in the setting of hyponatremia, urinary retention, fever, dysphagia. Placed on palliative care and died from dehydration. Two doses of donanemab, last dose 55 days prior to event. PMH of hypertension, diabetes mellitus type 2, hypercholesterolemia
15T-MC-AACI- (b) (6) (b) (6)	69F	3	Death due to pulmonary embolism; attributed to "immobility due to Alzheimer's disease" 1 dose; last dose on Day 1. PMH of hypertension, hyperlipidemia, diabetes mellitus type 2, hereditary spherocytosis, mitral valve prolapse, atrial fibrillation, and sleep apnea

Subject ID	Age/Sex	Study Day Onset	Brief Narrative (Fatal AE term in bold)
15T-MC-AACI- (b) (6) (b) (6)	81F	215	Pulmonary embolism 6 doses; last dose day 141. PMH: concomitant med of raloxifene that has boxed warning for pulmonary embolism.
15T-MC-AACI- (b) (6) (b) (6)	84F	154	Dementia, Alzheimer's type 1 month post SAE of acute myocardial infarction on Study Day 103. Developed severe esophagitis with gastric erosions. Refused to take medications and sent to hospice. 3 doses; last dose day 98. PMH: gastroesophageal reflux disease, hypertension, hyperlipidemia
15T-MC-AACI- (b) (6) (b) (6)	63M	174	Completed Suicide. In the two weeks preceding the event, he was noted to be more paranoid, anxious, confused, and had worsening vision and delusional behavior. 6 doses; last dose Day 140 PMH of one episode of paranoia/delusion, circadian sleep disorder, hypothyroidism, obstructive sleep apnea
15T-MC-AACI- (b) (6) (b) (6)	75M	314	Completed Suicide 12 doses; last dose Day 309 PMH of depression
15T-MC-AACI- (b) (6) (b) (6)	82F	267	Presented with abdominal pain and was diagnosed with retroperitoneal hemorrhage. Renal failure worsened, also with thrombocytopenia. 10 doses; last dose Day 255 PMH: atrial fibrillation on warfarin; renal failure
15T-MC-AACI- (b) (6) (b) (6)	83F	63	"Death". No information. Subject died in her sleep. 2 doses; last dose Day 29 PMH: hypertension, hyperlipidemia. Concomitant meds include alprazolam.

Subject ID	Age/Sex	Study Day Onset	Brief Narrative (Fatal AE term in bold)
I5T-MC-AACI- (b) (6)	72M	331	Respiratory arrest in the setting of concurrent events of gastric outlet obstruction suspected to be secondary to metastatic disease, pancreatitis, and severe right hydronephrosis secondary to right ureteropelvic junction obstruction 11 doses; last dose Day 281
I5T-MC-AACG- (b) (6)	85F	36	Pneumonia Event onset: 4 days after the 2nd dose. PMH of CAD s/p CABG, HTN, TIA, nephropathy, moderate dementia.
I5T-MC-AACI- (b) (6)	75F	514	Respiratory failure occurring in the hospital. 13 doses; last dose Day 330 PMH: hypertension, cholelithiasis, gastritis, stomach polyp, diverticular disease, colorectal adenomatous polyps, chronic kidney disease, venous thrombosis, varicose veins, benign supraventricular arrhythmias, dizziness, bradycardia
I5T-MC-AACI- (b) (6)	85F	214	SAE of pneumonia (severe) beginning on Day 196. 2 doses; last dose on Study day 28 PMH: hypercholesterolemia, cerebrovascular accident, urinary incontinence, bilateral carotid endarterectomy, naproxen allergy, pernicious anemia
* I5T-MC-AACG- (b) (6)	76M	775	Death with verbatim term "Death (Unknown cause of death)." The cause of the death and autopsy status were reported to be unknown. 14 donanemab doses (last donanemab dose on Study Day 365) PMH of atrial fibrillation, bradycardia, coronary artery disease, hyperlipidemia, hypertension, SAE of acute encephalopathy on SD 140 of unclear etiology (27 days after 5th dose)

Subject ID	Age/Sex	Study Day Onset	Brief Narrative (Fatal AE term in bold)
* 15T-MC-AACI- (b) (6)	81F	536	"Death". Multiple fractures from unwitnessed fall in an apartment in an assisted living facility on Day 524. 19 doses; last dose day 499
* 15T-MC-AACI- (b) (6)	75F	466	Admitted to the hospital for carotid endarterectomy and experienced a cerebrovascular accident on Day 466. Died 4 months later. 17 doses; last dose Day 445 PMH: ApoE e3/e3 status, coronary artery disease, carotid artery occlusion, hypertension, hyperlipidemia, atrial fibrillation

*Deaths occurred after Week 76.

At the time of the 90-Day Safety Update, an additional 19 deaths were reported among donanemab-treated subjects in the all-donanemab pool. Based on 37 cases, the incidence of adverse events with fatal outcome in the all-donanemab pool was 1.3% (37/2802) using an on-study approach. Additional deaths in the all-donanemab pool, are shown in the following tableTable 12.

Table 12. Additional Deaths in the All-donanemab Pool, On-Study Approach

Subject ID	Age/Sex	Study Day Onset	Brief Narrative (Fatal AE term in bold)
15T-MC-AACI- (b) (6)	77M	694	Hospitalized for difficulty walking, worsening confusion, severe headache, severe nausea, severe dizziness, severe unstable gait, and severe visual impairment and with the SAE of ARIA-E (severe), aggravated by seizures. Received 5 doses of donanemab; last dose on study day 671 PMH: ApoE ε3/ε4, hypertension, hyperlipidemia, coronary artery disease, atrial flutter, prostate cancer
15T-MC-AACI- (b) (6) 8	70M	702	Developed headache and slurred speech and was hospitalized for the SAE of ischemic stroke (severe).

Subject ID	Age/Sex	Study Day Onset	Brief Narrative (Fatal AE term in bold)
			Ischemic changes not observed on CT. Tenecteplase administered, resulting in SAE of intracranial hemorrhage (severe), with ARIA-E (severe), superficial siderosis. Death due to bilateral intraparenchymal hemorrhage and acute hypoxic respiratory failure. 5 doses; last dose on Study day 693. PMH: ApoE ε3/ε4, and dyspepsia
I5T-MC-AACI- (b) (6)	77M	409	Unable to ambulate, had right sided weakness, had ongoing confusion and aphasia, blood pressure of 170/92 mmHg on arrival, developed the SAE of thalamus hemorrhage (severe), having fallen on the previous day. The hospital course included development of an upper gastrointestinal bleed and respiratory distress due to presumed aspiration event from emergent intubation and dysphagia. Discharged to hospice. 14 doses; last dose day 370 PMH: ApoE ε3/ε4, diabetes mellitus, hyperlipidemia, hypertension, parkinsonism, restless leg syndrome, aphasia and stroke
I5T-MC-AACI- (b) (6)	75F	38	The acute respiratory failure occurred in the setting of multifocal pneumonia. 2 doses; last dose Day 32 PMH of COPD
I5T-MC-AACI- (b) (6)	84M	282	Severe respiratory failure as a complication from stent placement for carotid artery disease 10 doses; last dose day 258 PMH of coronary artery disease, s/p coronary artery bypass graft, congestive heart failure, atrial fibrillation, aortic valve replacement, gastroesophageal reflux disease, hypertension, hyperlipidemia, pulmonary hypertension
I5T-MC-	86M	335	Complications of blunt force head injury after a fall.

Subject ID	Age/Sex	Study Day Onset	Brief Narrative (Fatal AE term in bold)
AACI- (b) (6) (b) (6)			12 doses; last dose Day 312 PMH: hypertension, coronary artery bypass, blood cholesterol increased, osteoarthritis, glomerulonephritis, atrial fibrillation, glaucoma, benign prostatic hyperplasia. Concomitant meds include warfarin
I5T-MC-AACG- (b) (6) (b) (6)	76M	438	Congestive heart failure (severe) subsequent to progressive weakness. 9 doses; last donanemab dose on day 229 PMH: cardiomyopathy, left ventricular failure, hyperlipidemia, diabetes mellitus type 2, ventricular extrasystoles.
I5T-MC-AACI- (b) (6) (b) (6)	79M	427	Worsening of Pancreatic carcinoma, metastatic approximately 2 months after diagnosis of metastatic pancreatic carcinoma (SD 370). 14 doses; last dose day 372 h/o tobacco use and diabetes mellitus;
I5T-MC-AACI- (b) (6) (b) (6)	77F	408	Presented with severe hypokalemia which led to atrial fibrillation and hospitalization, requiring CPR; severe aspiration pneumonia 12 doses; last dose day 365 PMH: coronary artery disease, gastroesophageal reflux disease, hyperlipidemia, hypertension, rheumatoid arthritis, diabetes mellitus type 2, mild dementia.
I5T-MC-AACI- (b) (6) (b) (6)	80M	204	Lack of information on the cause of unwitnessed death. An autopsy was not performed. 7 doses; last dose day 173 PMH: Attention deficit hyperactivity disorder, chronic obstructive pulmonary disease, coronary artery disease, stent placement, diabetes mellitus type 2, Chronic lymphocytic leukemia, recurrent falls, sleep apnea.

Subject ID	Age/Sex	Study Day Onset	Brief Narrative (Fatal AE term in bold)
I5T-MC-AACG- (b) (6)	77M	545-550	Stopped eating; on hospice; death due to metabolic encephalopathy. AE onset more than 125 days after the most recent dose of donanemab.
I5T-MC-AACI- (b) (6)	84M	660	SAEs of Aortic dissection and cardiac arrest reported on Day 660. Reported to be healthy up to time of event. Last dose of donanemab on Day 146. Last dose of placebo in long term extension on Day 657. PMH: aortic aneurysm, hypertension and dyslipidemia.
I5T-MC-AACI- (b) (6)	83M	41	Gunshot wound; shot by another person with a shotgun. 2 doses; last dose study Day 29.
I5T-MC-AACI- (b) (6)	70F	329	Developed severe dysphagia, approximately 4 days after botulinum toxin for cervical dystonia. Approximately 1 month later, death due to Lewy body dementia. 7 doses; last dose Study Day 173 PMH: Lewy body dementia, Parkinsonism, cervical dystonia, dysphagia, hypertension, mood swings, neurogenic cough, paranoia, and other.
I5T-MC-AACI- (b) (6)	75F	424	Cardiac arrest 8 doses; last dose Day 244 PMH: hypertension, hyperlipidemia (concurrent meds of atenolol, hydrochlorothiazide, isosorbide, ASA low dose)
I5T-MC-AACI- (b) (6)	81M	287	Fall caused by “startled sound,” resulted in pelvic fracture on Day 287. 7 doses; last dose Day 171 PMH: included atrial fibrillation, shattered elbow, macular degeneration, pulmonary hypertension, chronic obstructive pulmonary disease,

Subject ID	Age/Sex	Study Day Onset	Brief Narrative (Fatal AE term in bold)
			osteoporosis.
I5T-MC-AACI- (b) (6) (b) (6)	65F	689	Presented with SAEs of renal failure and urinary tract infection, following dysuria for 3 weeks, hallucinations for 5 days, vomiting for 2 days, and loss of appetite. Discharged to hospice. 2 doses; last dose day 657 PMH: hypertension, hyperlipidemia, migraine, anxiety, visual hallucinations
I5T-MC-AACI- (b) (6) (b) (6)	85F	627	Hospitalized due to dehydration, malnutrition and electrolyte imbalance and arrhythmias (severe). 14 doses of donanemab; last dose of donanemab on Day 374^a; last dose of placebo on Day 624. PMH: hypertension, degeneration of the lumbar spine joint, degeneration of the knee joints, depression
I5T-MC-AACI- (b) (6) (b) (6)	74F	323	The subject was diagnosed with the SAE of adenocarcinoma of the colon on SD 121 (8 days after the 5th dose [also the last dose]). Treatment was discontinued on SD 211 because of the adenocarcinoma of the colon. On Study Day 323, the subject experienced the SAEs of cardio-respiratory arrest, myocardial infarction, cardiac tamponade, pericardial effusion, and pulmonary embolism. 5 donanemab doses (last donanemab dose on Study Day 113) PMH included anemia, gastrointestinal obstruction, colectomy, abdominal hernia repair, myocardial infarction, hypertension, dyslipidemia, left bundle branch block, psoriasis, restrictive pulmonary disease, sleep apnea.

^aDonanemab doses as noted in ADEX dataset

This reviewer reviewed the narratives of all deaths in donanemab-treated subjects.

Clinical Review
Natalie Branagan, MD
BLA 761248
Kisunla/donanemab

Deaths from ARIA (subjects I5T-MC-AACI- (b) (6) I5T-MC-AACI- (b) (6) and I5T-MC-AACI- (b) (6)) are attributed to use of donanemab.

The role of donanemab in two subject with intracerebral hemorrhage (I5T-MC-AACI- (b) (6) in the setting of ARIA E and ARIA H, and I5T-MC-AACI- (b) (6)) cannot be ruled out, given the higher observed incidence of intracerebral hemorrhage > 1 cm in the placebo-controlled period of AACI (the reader is referred to the [ARIA and Intracerebral Hemorrhage > 1 cm section](#) for further details). However, the subjects had risk factors for CAA, which is associated with intracerebral hemorrhage, and in one case, the subject was administered thrombolytic therapy in the setting of ARIA-E.

Narratives for events of ARIA and intracerebral hemorrhage are provided below as well as one fatal event of thalamus hemorrhage. A summary of adverse events with fatal outcomes in the [placebo-controlled pool](#) and in the [all-donanemab pool](#) are shown in the appendix, and narratives of other selected deaths are provided in the [Appendix](#).

ARIA-E, I5T-MC-AACI- (b) (6)

72-year-old White female ApoE ε3/ε4 genotype with history of AD, chronic renal failure (glomerular filtration rate adjusted for body, sex, and age of 55 mL/min/1.73m² at baseline), open-reduction internal fixation of the knee, situational anxiety was hospitalized on Study Day 66 after presenting with confusion, agitation, forgetfulness, short attention span, garbled speech, and disorientation, and reporting the SAE of ARIA-E (severe). The subject was noted to have declining cognition for several weeks prior to the onset of ARIA-E. In the ER, body temperature was 37.3 Celsius, blood pressure 124/87 (units unspecified), respiratory rate was 16 (units unspecified), heart rate was 88 (units unspecified), and pulse oximetry 97 (units unspecified). The subject was admitted to the hospital and a CT scan of the head showed severe vasogenic edema. A repeat head CT scan that day showed: extensive vasogenic edema throughout the right cerebral hemisphere, and probably some within the left occipital lobe remains stable with no discrete enhancing mass. The last dose of donanemab (third dose) was on Study Day 56.

A CT angiograph without contrast showed a potential subacute right-sided stroke and multifocal areas of vasogenic edema in the right cerebral hemisphere with some confluence and mass effect. A CT angiogram of the head and neck showed a nonspecific multifocal area of vasogenic edema in the right cerebral hemisphere. Concomitant medications included escitalopram oxalate, ginkgo biloba, iron, zinc, vitamin K, vitamin D, coconut oil, and vitamin B12. The subject's treatment for her symptoms included dexamethasone 10 mg, followed by 4 mg twice daily, and levetiracetam 500 mg.

An EEG impression on Study Day 69 noted the following: "Abnormal EEG (abnormality grade

3/5). This EEG was diffusely and continually abnormal, consistent with the subject's clinical presentation of nonspecific moderately severe encephalopathy.”

On Study Day 72, a CT scan of the head showed extensive vasogenic edema throughout the right cerebral hemisphere, and probably some within the left occipital lobe that remained stable with no discrete enhancing mass, and the new finding of a sliver of hyperdensity within the right posterior and anterior frontal lobe sulci along the vertex suspicious for new foci of subarachnoid hemorrhage. The investigator notes that no MRI reports were received.

Three days later, the subject was discharged to hospice care. On Study Day 80, the subject died due to the event of ARIA. The death certificate listed the cause of death as cerebral edema. The outcome of ARIA-E was listed as fatal per the study investigator. An autopsy was performed; however, the results were not made available to the site.

The subject's screening MRI showed focal lesions of white matter disease and did not show presence of ARIA-E, cerebral microhemorrhages, cerebral hemorrhages, or superficial siderosis. The Applicant assessed the event of fatal ARIA-E as reasonably possibly related to donanemab ARIA-E is an expected event.

Reviewer comment: Although there are no post-screening MRIs in this case, in an email communication dated August 9, 2022, Dr. Ranjit Mani noted that the description of the brain CT is consistent with ARIA-E. This reviewer notes that the subject's death appears to be related to ARIA-E given the findings on the CT of the head.

Death, ARIA-E, and ARIA-H, I5T-MC-AACI- (b) (6)

This is a 75 year-old White male with a history including chronic kidney disease stage 3, hypertension, hyperlipidemia, type 2 diabetes mellitus, aortic arteriosclerosis, balance disorder, and heterozygous for ApoE ε4 who presented to the ER (on Study Day 427) with nausea (moderate) and vomiting (moderate) and was admitted for serious ARIA-E (severe) and ARIA-H (severe). The subject died 18 days later.²⁴ On Study Day 413, severe ARIA-E was reported and the subject was reported to experience confusional state (moderate) and balance disorder (moderate). The subject had received 10 doses of donanemab prior to presentation to the ER, with the most recent dose occurring on Study Day 399. Concomitant medications included ascorbic acid, carvedilol, cholecalciferol, duloxetine, hydrochlorothiazide/olmesartan, iron, memantine, metformin, pantoprazole, rosuvastatin, tamsulosin, and vitamin B complex. An unscheduled MRI obtained four days before presentation to the ER (Study Day 423) showed severe ARIA-E (right frontal; left frontal; right temporal, right occipital, right parietal; left

²⁴ Information for the narrative noted in the Applicant's submissions to IND 109157 on December 23, 2022, December 28, 2022, January 3, 2023, and January 5, 2023.

parietal;) and more than 10 new microhemorrhages (43 total microhemorrhages). At baseline, the subject's MRI showed no ARIA-E, microhemorrhages, superficial siderosis, or intracerebral hemorrhage. Vital signs upon admission to the ER included an elevated blood pressure (213/107 [units not reported]), temperature 36.9 (units not reported), pulse of 75 (units not reported), and respiratory rate of 18 (units not reported). A neurological exam showed left-sided weakness with some contracture, left-sided neglect, altered mental status, and somnolence. The impression from a CT scan was diffuse vasogenic edema within the right cerebral hemisphere with 2 mm of right to left midline shift. An MRI the following day showed ARIA-E with extent greater than 10 cm and involvement in multiple areas of the brain (right frontal, right temporal, non-hippocampal, right parietal, right occipital, left frontal, left parietal) and greater than 10 microhemorrhages. The subject was started on dexamethasone and ondansetron and discharged to hospice that day (Study Day 428). Ten days later, he was discharged to a skilled nursing facility where he passed 9 days later (SAE preferred term: death). He was also reported to die due to symptomatic ARIA-E and symptomatic ARIA-H. No autopsy was performed.

Additional events experienced by the subject and not included above are outlined in the table below.

Table 13. Additional Events Occurring in Subject (b) (6) in Main Study AACI.

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

Study Day	Events
331	Starting with 8 th infusion, the dose was adjusted to 1400 mg.
427	Presentation to ER for current event after receiving 10 donanemab infusions

Reviewer comment: This reviewer assessed the subject's death as related to ARIA. A role for donanemab in the SAE is likely, given that ARIA is among the most frequently reported TEAEs in donanemab-treated subjects in the placebo-controlled pool and a known risk with monoclonal antibodies directed against aggregated forms of beta amyloid.

ARIA-E (initially reported as cerebrovascular accident), I5T-MC-AACI- (b) (6)²⁵

77 year-old male with past medical history of AD, hypertension, hyperlipidemia, coronary artery disease, atrial flutter, prostate cancer, ApoE ε3/ε4 genotype, who was hospitalized for difficulty walking, worsening confusion, severe headache, severe nausea, severe dizziness, severe unstable gait, and severe visual impairment on Study Day 694 and with the SAE of ARIA-E (severe). He had received his fifth dose of donanemab 23 days before hospitalization. An MRI on Study Day 696 showed moderate T2 hyperintense lesion in the right occipital lobe with vasogenic edema and mild mass effect. Two days later, the subject was transferred to another hospital and experienced hypoxia, was transferred into the intensive care unit, and was obtunded. He was reported to have seizures (generalized seizure, episodes of arm tremor that looked like seizure, and episodes of gaze deviation suggestive of seizure). The following day, he was started on intravenous methylprednisolone 1000 mg/day for five days and then prednisone 60 mg daily. During the hospitalization, he also received acyclovir, levetiracetam, lorazepam, valproic acid, and lacosamide. He underwent a lumbar puncture, which yielded 3 mL of cerebrospinal fluid (CSF), with findings of protein 104, glucose 80, white blood cells 23, red blood cells 3200 (reference ranges not provided). A repeat lumbar puncture showed two nucleated cells and was negative for herpes simplex virus. Serum and CSF autoimmune encephalitis panels were negative and serum John Cunningham (JC) virus was positive. CSF JC virus testing was not performed. On Study Day 716, he was discharged to hospice and then returned the same day for comfort care because of worsening obtundation and near comatose state. Seven days later (Study Day 723), an MRI showed decreased abnormal T2/FLAIR signal in the right occipital lobe with resolution of surrounding mass effect and sulcal effacement. Five days later, he was discharged to a nursing home and two days later he died (Study Day 730). The cause of death was reported as secondary to symptomatic ARIA-E, aggravated by seizures. His screening MRI showed 1 microhemorrhage. The most recent MRI prior to the SAE of ARIA-E was on Study Day 631 and did not show any new microhemorrhages or presence of ARIA-E. Concomitant medications included atorvastatin, acetylsalicylic acid, vitamin D3, donepezil, lisinopril, calcium carbonate, fish oil, hericium erinaceus mycelium, dimethylethanolamine,

²⁵ Patient was from the all-donanemab pool. Information taken from the Medwatch report submitted by the Applicant under IND 109157 dated May 30, 2023.

multivitamin, ubidecarenone and pyrroloquinoline quinone.

Reviewer comment: A role for donanemab in this case of ARIA-E with fatal outcome is likely given the development of ARIA-E while on treatment with donanemab.

Intracerebral hemorrhage in the setting of ARIA-E and ARIA-H, I5T-MC-AACI- (b) (6)

This is a 72-year-old White male, ApoE $\epsilon 3/\epsilon 3$ genotype, with bowel cancer, history of brain trauma, migraines, hypertension, hypercholesterolemia, who was hospitalized for right hemiplegia and aphasia on Study Day 72 and was diagnosed with severe intracerebral hemorrhage and hemorrhagic stroke with mass effect. The SAE of ARIA-H (severe) was also reported that day. The subject had taken several acetylsalicylic acid tablets (quantity and dose unknown) at the onset of his speech aphasia. The last dose of donanemab had been 43 days before (Study Day 29), and he had received 2 doses of study drug. Concomitant medications included atorvastatin, cetirizine, cholecalciferol, dexamethasone eye drops, dextrin, donepezil, fesoterodine, ibuprofen, levothyroxine, melatonin, paracetamol, tamsulosin, and vitamin B1. Prior to the event, he had complained of a mild headache on Study Days 46 through 56, and on Study Day 59. On Study Day 46, the subject was reported to have mild ARIA-E. Blood pressures ranged between 106 to 135/65 to 73 mmHg during his study visits prior to the event of intracerebral hemorrhage.

On Study Day 62, the study site recommended that he get an MRI sooner than the MRI scheduled for Study Day 71; however, the subject declined, citing an upcoming cataract surgery that contraindicated MRIs be done within 5 days of the surgery. An MRI performed on Study Day 71, one day prior to his hospitalization, showed mild ARIA-E (left parietal, right occipital, and right temporal lobes), ARIA-H (based on presence of a new microhemorrhage), superficial siderosis in the left frontal lobe (increased from baseline of 50 mm to 65 mm), and superficial siderosis in the right occipital, right parietal, and right temporal non-hippocampal (all measuring < 8 mm). Approximately four months before his screening MRI, the subject had an MRI that showed "hemorrhagic focal area left caudate nucleus (cavernoma?)." Three weeks later a CT angiography showed no arteriovenous malformation. His screening MRI had shown superficial siderosis in the left frontal lobe (50 mm) and presence of white matter disease with beginning of confluence of lesions according to the central read, with the local read of the MRI noting moderate to marked amount of increased T2 signal identified in the periventricular, deep and subcortical white matter of both cerebral hemispheres, possible small area of vasogenic edema in the left parieto-occipital lobe, and suspected small old infarct in the inferior left cerebellum. Vital signs in the ER showed a heart rate of 59 (units unspecified), blood pressure 140/82 (units not specified), respiratory rate of 16 (units not specified), saturation of 97%, glucose 6.2 (units not specified). Physical exam showed right hemineglect, right hemiplegia, regular heart sounds, and low limb exam noted as stroke. He then developed sudden aphasia and right hemiplegia and was seen by neurology and neurosurgery. A CT scan in

the ER showed a large left parietal intraparenchymal hemorrhage and vasogenic edema, left frontotemporoparietal intraparenchymal hemorrhage of amyloid appearance with midline shift (5mm), and an adjacent subarachnoid hemorrhage. A repeat CT scan the same day showed a hematoma in the left posterior parietal region, measuring 5.5 x 4.3 cm. A CT angiogram of the carotid arteries showed < 50% stenosis of the left carotid artery and < 30% of the right carotid artery. The platelet count, internationalized normal ratio (INR), and the activated partial thromboplastin time (PTT) were normal (platelets $144 \times 10^9/L$ [$130-400 \times 10^9$], INR 1 [reference range not provided], PTT 22.9 sec [20.5-27.5]) and the potassium and creatinine kinase was slightly elevated (potassium 5.4 mmol/l [3.5-5.1] and CK 207 u/L [55-170]). Neurosurgery offered surgery for the purpose of decompression; however, his spouse decided upon palliative care and his condition deteriorated later that day (Study Day 72). He became comatose, was transferred to palliative care, and died on Study Day 75. The cause of death on the death certificate was hemorrhagic stroke and ARIA-H. An autopsy was not performed.

Reviewer comment: This reviewer notes that the subject's death appears to be related to the intracerebral hemorrhage associated with the findings on the MRI of the brain of ARIA-E and ARIA-H one day prior to his hospitalization. In an email communication dated August 9, 2022, Dr. Mani noted that hemorrhages due to cerebral cavernomas are rarely very large, and the hemorrhage that this subject experienced may be more consistent with an ARIA-related intracerebral hemorrhage. In a review of the screening MRI and Study Day 71 MRI at a meeting dated September 9, 2022, Dr. Ranjit Mani assessed the cavernous malformation noted on the screening MRI as unlikely to have contributed to the bleed, given the difference in areas of the brain that were affected. The ingestion of acetylsalicylic acid prior to the event of intracerebral hemorrhage may have also contributed to worsening of the outcome of the event. This subject may have had cerebral amyloid angiopathy given findings on screening MRI of superficial siderosis and white matter disease, which can be seen with cerebral amyloid angiopathy.²⁶ CAA is a risk factor for intracerebral hemorrhage in subjects with Alzheimer's disease.²⁷

Intracerebral Hemorrhage (reported preferred term was Intracranial Hemorrhage), I5T-MC-AACI- (b) (6)

A 70 year-old male with past medical history of AD, ApoE $\epsilon 3/\epsilon 4$ carrier, and dyspepsia, and screening MRI showing focal lesions of white matter disease, who developed headache and slurred speech and was hospitalized for the SAE of ischemic stroke (severe) on Study Day 702, 9 days after the 5th dose of donanemab. Blood pressure on admission was 146/83 mmHg with a

²⁶ Charidimou A, Boulouis G, Frosch M. The Boston criteria version 2.0 for cerebral amyloid angiopathy: a multicentre, retrospective, MRI-neuropathology diagnostic accuracy study. *Lancet Neurol*. 2022 Aug;21(8):714-725. doi: 10.1016/S1474-4422(22)00208-3.

²⁷ Ringman JM, Sachs MC, Zhou Y. Angiopathy and influence of APOE Genotype in Persons with Pathologically Verified Alzheimer Disease. *JAMA Neurol* 2014; 71:878-883. doi:10.1001/jamaneurol.2014.681

heart rate of 65 beats per minute. An ECG showed sinus rhythm. Labs showed a normal international normalized ratio (0.98, reference range of 0.86-1.09) and normal activated partial thromboplastin time (22.9 sec, reference range 22.1 - 33.9). The most recent study blood pressure reading (9 days prior to the ischemic stroke) had been normal at 122/77 mmHg. Blood pressures readings at study visits when the subject was on treatment with donanemab ranged between 113-133/68-77 mmHg (Visits 23 through 26). Concomitant medications at the time of the event included alprazolam, escitalopram, memantine, pantoprazole, and vitamin D. A CT angiogram of the head and neck vessels did not show significant stenosis, dissection, aneurysm, or large vessel occlusion. A CT of the head/brain without contrast did not identify an acute intracranial process. A CT brain perfusion showed no asymmetric fixed or reversible ischemic defect. A tele-neurology consult recommended that the subject receive tissue plasminogen activator (tPA). An hour after receiving tenecteplase, the subject developed altered mental status. A repeat CT scan showed multiple hemorrhages in the bilateral hemispheres. The SAE of intracranial hemorrhage was reported (severe). The subject was given factor I, factor VIII, factor XIII and Von Willebrand factor to reverse the effect of tenecteplase. An MRI performed after tenecteplase administration (centrally read) showed presence of severe ARIA-E in the left parietal lobe and bilateral frontal and occipital lobes; superficial siderosis in the left parietal (70 mm), occipital (50 mm), and temporal (40 mm) lobes; macrohemorrhage in the left temporal lobe (50 mm), left occipital (50 mm), left parietal (35 mm), and right frontal (30 mm); and bilateral intraventricular hemorrhage. On the same day (Study Day 702), the SAE of ARIA-E (severe) was reported. Four days later, the subject died due to bilateral intraparenchymal hemorrhage and acute hypoxic respiratory failure. No autopsy was performed. The most recent MRI prior to the SAE of intracranial hemorrhage was on Study Day 663 and showed focal lesions of white matter disease.

Reviewer comment: Thrombolytic use is a risk factor for intracerebral hemorrhage in this case. Additionally, this subject was heterozygous for ApoE ε4; the presence of an ApoE ε4 has been associated with intracerebral hemorrhage.²⁸ The case is notable in that the subject presented with ischemic symptoms and was found to have ARIA-E, which can present with focal neurological deficits. Prior to administering thrombolytics, consideration should be taken into whether ARIA may be the potential cause for stroke-like symptoms in patients treated with donanemab. The presence of superficial siderosis may be consistent with CAA, which is a risk factor for intracerebral hemorrhage. The relationship of intracerebral hemorrhage to donanemab in this setting of treatment with tenecteplase is uncertain.

Thalamus hemorrhage, IST-MC-AACI- (b) (6)

A 77 year-old male with history of ApoE ε3/ε4 carrier, diabetes mellitus, hyperlipidemia,

²⁸ Marini S, Crawford K, Morotti A, et al. Association of Apolipoprotein E With Intracerebral Hemorrhage Risk by Race/Ethnicity: A Meta-analysis JAMA Neurol. 2019 Apr 1;76(4):480-491. doi: 10.1001/jamaneurol.2018.4519.

hypertension, parkinsonism, restless leg syndrome, aphasia and stroke who developed the SAE of thalamus hemorrhage (severe) on Study Day 409 and died on Study Day 421. On the day of hospitalization, the subject was unable to ambulate, had right sided weakness, and had ongoing confusion and aphasia and had a blood pressure of 170/92 mmHg on arrival (136/72 mmHg at the most recent study visit on Study Day 370).²⁹ The day before, the subject attempted to get up after dinner and had fallen. The subject had received a tetanus shot and Covid booster on Study Day 408 (also reported as Study Day 407). A head CT on Study Day 409 showed an acute left thalamic hemorrhage measuring 2.2 cm with some minimal surrounding edema. The most recent dose of study drug had been 39 days prior to the SAE of thalamus hemorrhage (14th dose of donanemab) at which point the subject was discontinued from treatment after having met dose-stopping criteria. Baseline MRI showed beginning confluence of white matter disease. No new findings from baseline were reported on the subject's last MRI in the study, which occurred on Study Day 364. Concomitant medications included carbidopa, doxazosin, fluticasone, glargine, levodopa, metformin; sitagliptin, metoprolol, potassium, and sildenafil. A head CT the following day showed stable thalamic hemorrhage with surrounding edema and intraventricular hemorrhage layering within the posterior horns of the lateral ventricles. The hospital course included development of an upper gastrointestinal bleed and respiratory distress due to presumed aspiration event from emergent intubation and dysphagia. On Study Day 418, the subject was discharged to home hospice, and on Study Day 421, the subject died due to thalamus hemorrhage. An autopsy was not performed.

Reviewer comment: This subject had past medical history of hypertension, which is a risk factor for thalamic hemorrhage, and a role for donanemab in the event of thalamus hemorrhage cannot be established.

8.4.2. Serious Adverse Events

In the placebo-controlled period of AACI, serious adverse events (SAEs) occurring within 57 days of the last dose were reported in 16.4% (140/853) of donanemab-treated subjects compared to 14.2% (124/874) of placebo-treated subjects. These findings are consistent with the Applicant's prespecified approach of analyzing adverse events occurring within the treatment period plus 57 days in which SAEs occurred in 17% of donanemab-treated subjects and 15% of placebo-treated subjects in the placebo-controlled period of AACI. In the placebo-controlled pool, the incidence of SAEs was 16.5% (162/984) in donanemab-treated subjects and 14.3% (143/999) placebo-treated subjects (see the following table). The system organ class (SOC) category with the highest incidence of SAEs in the donanemab arm and greater than placebo was Nervous system disorders (4.5%, driven by ARIA-E).

The placebo-controlled pool is presented in the table below to allow for capturing of more rare

²⁹ Noted in the Applicant's response dated August 28, 2023, to an information request dated August 25, 2023.

events. The SAEs with the greatest incidence in the placebo-controlled pool, reported in 2 or more subjects receiving donanemab and greater than placebo were ARIA-E (1.5% vs 0), pneumonia (1% vs 0.3%), Intracranial Hemorrhage (0.7% vs 0.2%), Covid 19 (0.7% vs 0.4%), Allergic Reaction/Hypersensitivity (0.5% vs none) and intestinal obstruction (0.5% vs none) as shown in Tables 18 (for analysis by SOC) and Table 15 (for analysis by grouped terms). [ARIA and intracerebral hemorrhage](#), [seizure](#), [hypersensitivity and infusion reactions](#), and [intestinal obstruction/perforation](#) will be discussed in more detail as adverse events of special interest.

Table 14. SAEs Grouped by SOC with Preferred Terms with Incidence of at Least 0.2% Higher in the Donanemab Arm Compared to Placebo in the Placebo-controlled Pool

Preferred Terms By SOC	Donanemab N=984 n (%)	Placebo N=999 n (%)
Total Subjects with any SAEs	162 (16.5)	143 (14.3)
Nervous system disorders	44 (4.5)	28 (2.8)
Amyloid related imaging abnormality-edema/effusion	15 (1.5)	0
Amyloid related imaging abnormality-microhemorrhages and hemosiderin deposits	4 (0.4)	0
Seizure	3 (0.3)	1 (0.1)
Gastrointestinal disorders	18 (1.8)	12 (1.2)
Small intestinal obstruction	4 (0.4)	0
Pancreatitis acute	2 (0.2)	0
Injury, poisoning and procedural complications	24 (2.4)	19 (1.9)
Subdural hematoma	4 (0.4)	0
Fall	4 (0.4)	1 (0.1)
Infusion related reaction	3 (0.3)	0
Infections and infestations	31 (3.2)	28 (2.8)
Pneumonia	10 (1)	3 (0.3)
Covid-19	7 (0.7)	4 (0.4)
Cardiac disorders	13 (1.3)	11 (1.1)
Acute myocardial infarction	4 (0.4)	0
Sinus node dysfunction	2 (0.2)	0
Metabolism and nutrition disorders	8 (0.8)	6 (0.6)
Dehydration	5 (0.5)	1 (0.1)
Reproductive system and breast disorders	3 (0.3)	0
Benign prostatic hyperplasia	2 (0.2)	0
General disorders and administration site conditions	6 (0.6)	5 (0.5)
Death	2 (0.2)	0
Respiratory, thoracic, and mediastinal disorders	10 (1)	8 (0.8)

Preferred Terms By SOC	Donanemab N=984 n (%)	Placebo N=999 n (%)
Pulmonary embolism	5 (0.5)	2 (0.2)
Pneumothorax	2 (0.2)	0
Psychiatric disorders	13 (1.3)	13 (1.3)
Agitation	4 (0.4)	2 (0.2)
Renal and urinary disorders	7 (0.7)	6 (0.6)
Acute kidney injury	4 (0.4)	2 (0.2)
Neoplasms benign, malignant, and unspecified	13 (1.3)	18 (1.8)
Plasma cell myeloma	2 (0.2)	0

This reviewer created this table using the 90-Day Safety IDB ADAE dataset, AESER = Y, TEPCLDL=Y, APERIODC= First treatment period.

The reviewer is referred to the [Appendix](#) for SAEs by preferred term in the placebo-controlled period of AACI and the placebo-controlled pool.

Table 15. SAEs by Grouped Terms with Incidence of at Least 0.2% Higher in the Donanemab Arm Compared to Placebo in the Placebo-controlled Pool

Grouped Terms	Donanemab N=984 n (%)	Placebo N=999 n (%)
Allergic Reaction, Hypersensitivity	5 (0.5)	0
Drug eruption	1 (0.1)	0
Infusion related reaction	3 (0.3)	0
Urticaria	1 (0.1)	0
Intestinal Obstruction	5 (0.5)	0
Small intestinal obstruction	4 (0.4)	0
Intestinal obstruction	1 (0.1)	0
Intracranial Hemorrhage	7 (0.7)	2 (0.2)
Extradural hematoma	1 (0.1)	0
Hemorrhagic stroke	1 (0.1)	1 (0.1)
Subarachnoid hemorrhage	2 (0.2)	1 (0.1)
Subdural hematoma	4 (0.4)	0
Chest Pain (Non-Cardiac Or Unknown)	5 (0.5)	2 (0.2)
Chest discomfort	1 (0.1)	0
Chest pain	1 (0.1)	1 (0.1)
Musculoskeletal chest pain	1 (0.1)	0
Non-cardiac chest pain	2 (0.2)	1 (0.1)
Gastritis, Duodenitis	2 (0.2)	0

Grouped Terms	Donanemab N=984 n (%)	Placebo N=999 n (%)
Duodenitis	1 (0.1)	0
Gastritis erosive	1 (0.1)	0
Colitis, Gastroenteritis	3 (0.3)	1 (0.1)
Clostridium difficile colitis	1 (0.1)	0
Colitis	1 (0.1)	0
Diarrhea	0	1 (0.1)
Gastroenteritis	1 (0.1)	0

This reviewer created this table using the 90-Day Safety IDB ADAE dataset, AESER = Y, TEPCDLFL.

The incidence of SAEs in the all-donanemab pool after the 90-Day Safety Update was 14% (393/2802). The most common SAEs were ARIA-E (1.1%, 32/2802), syncope (0.9%, 24/2802), pneumonia (0.6%, 18/2802), Covid-19 (0.6%, 17/2802), and fall (0.6%, 16/2802). In the all-donanemab pool, grouped SAEs with incidence of at least 1% were reported with infection (2.1%) and fracture (1.3%) ([Appendix](#)). The reader is referred to the [Appendix](#) for a list of preferred terms contributing to these groups in this submission.

There were no SAEs of agranulocytosis, aplastic anemia, bone marrow depression, disseminated intravascular coagulation, hemolytic anemia, liver failure, pancytopenia, Stevens Johnson syndrome, toxic epidermal necrolysis, rhabdomyolysis, sudden death, torsade, thrombotic thrombocytopenia purpura.

Selected narratives for SAEs can be found in the [Appendix](#).

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

In the placebo-controlled period of AACI, 29.9% (255/853) of donanemab-treated subjects discontinued treatment compared to 20.1% (176/874) of placebo-treated subjects. The reader is referred to the [Appendix](#) for a table with further details of treatment discontinuation in the placebo-controlled period of AACI. Based on analyses using the adverse event dataset, adverse events were reported to lead to treatment discontinuation in 13.0% (111/853) of donanemab-treated subjects compared to 4% on placebo (35/874).³⁰ Infusion related reactions and ARIA-E were the most frequent adverse events reported to lead to treatment discontinuation (see table below). Discontinuations because of infusion reactions and ARIA were in part driven by protocol-specified discontinuation criteria.

³⁰ Adverse events reported to lead to study withdrawal and treatment discontinuation were recorded in the adverse event dataset and the disposition dataset. This reviewer considered the adverse event dataset to be the more comprehensive source for recording adverse events reported to lead to study withdrawal or treatment discontinuation.

Using the adverse event database, adverse events lead to treatment discontinuation in 10.3% of subjects in the all-donanemab pool. Infusion related reaction and ARIA-E were the most frequently reported TEAEs leading to treatment discontinuation (occurring in 2.9% and 2.0 % of subjects, respectively). Similar findings were observed for the placebo-controlled pool. Please refer to [Appendix](#) for treatment discontinuation for the all-donanemab pool.

Table 16. TEAEs Reported to Lead to Treatment Discontinuation by Preferred Term with Incidence of at Least 0.2% Higher in the Donanemab Arm Compared to Placebo in the Placebo-Controlled Period of AACI

Preferred Terms	Donanemab (N = 853)	Placebo (N = 874)
Subjects with at least one AE Reported to Lead to Treatment Discontinuation	111 (13.0%)	35 (4.0%)
Infusion related reaction	31 (3.6%)	0 (0.0%)
Amyloid related imaging abnormality-edema/effusion	21 (2.5%)	3 (0.3%)
Amyloid related imaging abnormality-microhemorrhages and hemosiderin deposits	6 (0.7%)	2 (0.2%)
Hypersensitivity	4 (0.5%)	0 (0.0%)
Agitation	3 (0.4%)	0 (0.0%)
Anaphylactic reaction	3 (0.4%)	0 (0.0%)
Death	2 (0.2%)	0 (0.0%)
Delirium	2 (0.2%)	0 (0.0%)
Plasma cell myeloma	2 (0.2%)	0 (0.0%)
Pneumonia	2 (0.2%)	0 (0.0%)
Pulmonary embolism	2 (0.2%)	0 (0.0%)
Superficial siderosis of central nervous system	2 (0.2%)	0 (0.0%)
Syncope	2 (0.2%)	0 (0.0%)

This table was created by Senior Clinical Analyst Dr. Rui Li.

Study Withdrawal

In the placebo-controlled period of AACI, 26.5% (226/853) of donanemab-treated subjects and 19.9% (174/874) of placebo-treated subjects withdrew from the study. Based on analyses using the adverse event dataset, adverse events were reported to lead to study withdrawal with

higher incidence in the donanemab arm compared to placebo (7.9% (67/853) versus 3.3% (29/874), respectively).

Of note, vital status remained unknown for 22 subjects from the AACI placebo-controlled period that were lost to follow up (11 in placebo and 11 in donanemab). Among the donanemab-treated subjects, none had an ongoing SAE, none had an ongoing ARIA-E event, and among the 5 subjects with an ongoing ARIA- H event, none had macrohemorrhage, were serious, or were symptomatic.³¹

Refer to [Appendix](#) for further details regarding study withdrawal in the placebo-controlled period of AACI, the placebo-controlled pool, and the all-donanemab pool.

The reader is referred to the [Appendix](#) for narratives related to study withdrawal and treatment discontinuation.

In conclusion, adverse events leading to study discontinuation were reported with higher incidence in the donanemab arm compared to placebo (8% versus 3%, respectively). The incidence of participants lost to follow up in donanemab and placebo arms was balanced (1.3% for both). Infusion related reaction and ARIA-E were reported to lead to treatment discontinuation with highest incidence and greatest difference from placebo in the donanemab arm.

8.4.4. Significant Adverse Events

In Study AACI, the following severity scale was used to for categorization of adverse events. This reviewer found the severity scale used in AACI to be acceptable.

³¹ February 29, 2024, response to an information request.

Figure 3. Severity Scale for AEs Used in AACI

Assessment of Intensity
The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to one of the following categories: • Mild: An event that is easily tolerated by the participant, causing minimal discomfort, and not interfering with everyday activities. • Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities. • Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event, and both AEs and SAEs can be assessed as severe.

Taken from page 93 of the AACI protocol submitted June 12, 2023.

In Study AACG, categorization of intensity of AEs were conducted according to the principal investigator judgement.³² The reviewer notes that the lack of definitions for AE severity classification in Study AACG can result in inconsistent categorization of AE severity among principal investigators.

Definitions for mild, moderate, and severe categories for intensity of AEs were included in the protocols of the open-label studies.

Most TEAEs were mild or moderate in severity. A higher incidence of donanemab-treated subjects experienced severe TEAEs compared to placebo in AACI. Similar results were observed in the placebo-controlled pool. The following table shows the incidence of subjects experiencing at least one TEAE by mild, moderate, and severe categories in the placebo-controlled period of AACI.

Table 17. TEAEs by Maximum Severity Category in the Placebo-controlled Period of AACI.

Adverse Event Severity	DON N=853 n (%)	Placebo N=874 n (%)
Any TEAE	758 (88.9)	715 (81.8)
Subjects with Maximum AE Severity of Mild	308 (36.1)	327 (37.4)
Subjects with Maximum AE Severity of Moderate	352 (41.3)	313 (35.8)
Subjects with Maximum AE Severity of Severe	98 (11.5)	75 (8.6)

This table was created using analyses by Senior Clinical Analyst Dr. Rui Li using the adverse event dataset.

³² Noted in a response dated August 12, 2022, to an information request dated August 10, 2022.

The incidence of a subject having a TEAE with severity of severe was slightly lower in the all-donanemab pool compared to the placebo-controlled period of AACI (10.1% versus 11.5%, respectively). The lower incidence observed in the all-donanemab pool maybe due to selection bias as subjects who previously received donanemab and experienced mild intensity AEs may be more likely to continue to receive study drug compared to subjects who experienced severe intensity AEs.

ARIA-E and ARIA-H Microhemorrhage were among the most frequently reported TEAEs of severe severity in the placebo-controlled period of AACI. Similar results were observed in the placebo-controlled pool. The following table shows severe TEAEs in the placebo-controlled period of AACI.

Table 18. Severe TEAEs by Preferred Term with Incidence of at Least 0.3% Higher in the Donanemab Arm Compared to Placebo in the Placebo-controlled Period of AACI.

Adverse Event by Preferred Term	DON N=853 n (%)	Placebo N=874 n (%)
Amyloid related imaging abnormality-edema/effusion	14 (1.6)	0
Amyloid related imaging abnormality-microhemorrhages and hemosiderin deposits	4 (0.5)	0
Infusion related reaction	3 (0.4)	0
Pneumonia	3 (0.4)	0
Fall	4 (0.5)	1 (0.1)
Agitation	3 (0.4)	1 (0.1)

This table was created using analyses by Senior Clinical Analyst Dr. Rui Li using the adverse event dataset.

Similar to the placebo-controlled period of AACI, ARIA-E, infusion related reaction, and pneumonia were among the most frequently reported severe TEAEs reported in the all-donanemab pool (occurring at 1.6% for ARIA-E, and 0.4% for infusion related reaction and pneumonia).

The most frequent preferred terms of AEs with severe severity were also topics of interest identified in the Serious Adverse Events section of this review. The reader is referred to the Serious Adverse Events section of this review for further details related to these topics.

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

ARIA-E, ARIA-H Microhemorrhage, ARIA-H Superficial Siderosis, infusion related reaction, and headache were TEAEs reported with highest incidence in the donanemab arm and greatest difference from placebo in the placebo-controlled period of AACI. ARIA-E was reported in up to

24% of donanemab-treated subjects versus 2% on placebo. ARIA-H microhemorrhage occurred in up to 25% of donanemab-treated subjects compared to 11% on placebo. ARIA-H Superficial Siderosis occurred in up to 15% of donanemab-treated subjects compared to 3% on placebo. Infusion related reaction occurred in up to 9% of donanemab-treated subjects compared to 0.5% on placebo. TEAEs occurring in less than 5% of donanemab-treated subjects in the placebo-controlled period of AACI included pneumonia, chest discomfort, and flushing. In the all-donanemab-treated pool, ARIA-E, ARIA-H-Microhemorrhages, Covid-19, headache, and fall were among the most frequently reported TEAEs.

In AACG and AACI, ARIA events were recorded as adverse events and as MRI findings. ARIA-E findings were required to be reported as adverse events by investigators, but this was not specified for ARIA-H events. Because this reviewer considered the dataset containing MRI findings to be the more comprehensive dataset for ARIA findings, ARIA events for labeling purposes used incidences calculated using the MRI dataset. TEAEs associated with symptomatic ARIA are not included in the table of TEAEs.

ARIA-E, ARIA-H Microhemorrhage, ARIA-H Superficial siderosis, and Infusion related reaction, were among the most frequently reported TEAEs in the placebo-controlled period of AACI. The following table shows TEAEs by preferred term with incidence of at least 5% in the donanemab arm and at least 2% greater than placebo in the placebo-controlled period of AACI.

Table 19. TEAEs by Preferred Term Reported in at least 5% and at least 2% higher in the Donanemab Arm Compared to Placebo for Labeling in the Placebo-controlled Period of Study AACI.

Preferred Term	Donanemab N=853 n (%)	Placebo N=874 n (%)
Total Subjects with any TEAE	758 (88.9)	715 (81.8)
Amyloid related imaging abnormality-edema/effusion ^a	201 (23.6)	17 (1.9)
ARIA-H Microhemorrhage ^a	217 (25.4)	100 (11.4)
ARIA-H Superficial siderosis of central nervous system ^a	125 (14.7)	23 (2.6)
Infusion related reaction	74 (8.7)	4 (0.5)
Headache ^b	115 (13.5)	86 (9.8)

The reviewer created this using the IDB ADAE dataset submitted in the 90-Day Safety Update on September 11, 2023.

^aEvents related to ARIA are based on ARIA events reported in the MRI dataset and analyzed by Senior Clinical Analyst Dr. Rui Li.

^bThe term headache does not include headache associated with ARIA.

Less common adverse reactions in the placebo-controlled period of AACI are shown in the following table. This reviewer notes the following topics from the table below were included in

discussion in other sections of this review including pneumonia (Deaths and SAEs section of the Appendix), chest discomfort (noted as Non-cardiac Chest Pain in the SAEs section of the Appendix), and hypersensitivity (Hypersensitivity and Infusion Related Reactions section). The reader is referred to the Laboratory Findings section of this review for evaluations of hyponatremia and hypercholesterolemia. This reviewer did not identify a safety signal for hyponatremia or hypercholesterolemia based on analyses of lab findings in the placebo-controlled period of AACI or the placebo-controlled pool.

Table 20. TEAEs Reported in Fewer than 2% at Least 0.6% Higher and Odds Ratio > 2 in the Donanemab Arm Compared to Placebo in the Placebo-controlled Period of AACI

Preferred Term	Donanemab N=853 n (%)	Placebo N=874 n (%)
Chest discomfort	6 (0.7)	0
Flushing	5 (0.6)	0
Hypersensitivity	10 (1.2)	2 (0.2)
Grouped Terms Related to Hyponatremia	13 (1.5)	4 (0.5)
Hyponatremia	12 (1.4)	4 (0.5)
Blood sodium decreased	1 (0.1)	0
Rhinitis	8 (0.9)	3 (0.3)
Grouped Terms Related to Hypercholesterolemia	10 (1.2)	4 (0.5)
Hypercholesterolemia	8 (0.9)	2 (0.2)
Blood cholesterol increased	2 (0.2)	2 (0.2)
Urinary incontinence	15 (1.8)	6 (0.7)
Dental caries	9 (1.1)	4 (0.5)
Pneumonia	9 (1.1)	4 (0.5)
Rib fracture	9 (1.1)	4 (0.5)
Tinnitus	9 (1.1)	4 (0.5)

This reviewer created this table using the 90-Day Safety IDB ADAE dataset, TEPCLDLFL, APERIODC = First treatment period, STUDYID = AACI.

Similar findings of the incidence of ARIA-E, ARIA-H microhemorrhage, Infusion related reaction, and ARIA-H superficial siderosis were observed in the placebo-controlled pool as in the placebo-controlled period of AACI. The reader is referred to the [Appendix](#) for tables of TEAEs in the placebo-controlled pool.

ARIA-H microhemorrhage, ARIA-E, Covid-19, Superficial siderosis, Headache, and Fall were among the most frequently reported TEAEs in the all-donanemab pool. The following table shows TEAEs by preferred term with incidence of at least 5% in the all-donanemab pool.

Table 21. TEAEs by Preferred Term Reported in at Least 5% in the All-Donanemab Pool after the 90-Day Safety Update.

TEAEs by Preferred Term	Donanemab N=2802 n (%)
Total Subjects with Any TEAE	2188 (78.1)
Amyloid related imaging abnormality- microhemorrhages and hemosiderin deposits ^a	610 (21.8)
Amyloid related imaging abnormality- edema/effusion ^a	562 (20.1)
Covid-19	357 (12.7)
Superficial siderosis of central nervous system ^a	330 (11.8)
Headache ^b	298 (10.6)
Fall	291 (10.4)
Infusion related reaction	234 (8.4)

This reviewer created this table using the 90Day Safety IDB ADAE dataset, TELYLDFL.

^aEvents related to ARIA are based on ARIA events reported in the MRI dataset and analyzed by Senior Clinical Analyst Dr. Rui Li.

^bThe term headache does not include headache associated with ARIA.

The most frequent EMQ and FMQ groupings in the all-donanemab pool were infection and fall/dizziness/balance disorder. The reader is referred to the [Appendix](#) for a table showing TEAEs by EMQ and FMQ groupings with incidence of at least 5% in the all-donanemab pool.

8.4.6. Laboratory Findings

The reviewer did not identify any clinically meaningful changes in laboratory values in a review of analyses of mean change from baseline, shifts to high values, low values, and CTCAE toxicity Grades 3 through 4 for laboratory values related to chemistry or hematology, including laboratory findings related to TEAEs of hyponatremia, hypercholesterolemia, and hyperglycemia ([Appendix](#)). Additionally, this reviewer did not identify any clinically meaningful changes in a review of mean change from baseline and shift to abnormal for urine studies.

Differences no greater than 1% were observed in the incidence of TEAEs reported related to laboratory findings (hyponatremia, hypercholesterolemia, and hyperglycemia) in the donanemab arm and placebo arms of the placebo-controlled period of AACI.

There were no notable differences in the donanemab and placebo arms of the placebo-controlled pool for increases in AST and ALT, alkaline phosphatase, and bilirubin (difference no > 1%). No donanemab-treated subjects met Hy's Law.

Sodium

Although there was a higher incidence of TEAEs of hyponatremia in donanemab-treated subjects in the placebo-controlled period of AACI compared to placebo (1.5% versus 0.5%, respectively), there were no clinically meaningful changes in sodium detected after review of shift analyses.

Similar incidences of sodium shift to high and low were observed in the donanemab and placebo arms in the placebo-controlled pool (difference no greater than 0.2%). The following table shows shift to high and low values for sodium in the placebo-controlled pool.

Table 22. Sodium – Shifts to High and Low Values in the Placebo-Controlled Pool

Parameters	Shift	Donanemab (N = 984)	Placebo (N = 999)
SERUM Sodium (mmol/L)	Low or Normal to High	120 (12.2)	120 (12.0)
	High or Normal to Low	36 (3.7)	38 (3.8)

This table was created by Senior Clinical Analyst Dr. Rui Li.

Higher incidences of donanemab-treated subjects had decreases in sodium compared to placebo for a baseline of Grade 1 and shift to Grade 2 (1.2% versus 0.6%, respectively) or Grade 3 (0.2% versus none, respectively). The low number of subjects in these categories (n= < 15) limit the interpretability of this finding. A role for donanemab in one case of Grade 3 hyponatremia in could not be established as sodium levels returned to normal with continued donanemab dosing.³³ In a second case of Grade 3 hyponatremia, the subject's sodium level was noted to have improved while on therapy with donanemab.³⁴ The following table shows CTCAE shift to decrease for sodium in the placebo-controlled pool.

Table 23. CTCAE Shift to Decrease for Sodium (mmol/L) in the Placebo-Controlled Pool

Treatment	Baseline Tox. Grade	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Placebo	Grade 0	871 (89.2)	54 (5.5)	1 (0.1)	0 (0.0)	
	Grade 1	15 (1.5)	25 (2.6)	6 (0.6)	0 (0.0)	
	Grade 2	3 (0.3)	1 (0.1)	1 (0.1)	0 (0.0)	
Donanemab	Grade 0	846 (88.7)	50 (5.2)	4 (0.4)	0 (0.0)	
	Grade 1	14 (1.5)	26 (2.7)	11 (1.2)	2 (0.2)	
	Grade 2	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	

This table was created by Senior Clinical Analyst Dr. Rui Li.

Cholesterol

³³ I5T-MC-AACI- (b) (6)

³⁴ I5T-MC-AACI- (b) (6)

The incidence of TEAEs related to hypercholesterolemia was greater in donanemab-treated subjects compared to placebo in the placebo-controlled period of AACI (1.2% versus 0.5%, respectively). The reader is referred to the TEAEs and Adverse Reactions section of this review for further details. Similar findings were observed in the placebo-controlled pool (1.1% in the donanemab arm versus 0.4% on placebo, respectively).

Shifts to high and low values for cholesterol were similar for donanemab-treated subjects and placebo-treated subjects in the placebo-controlled pool (difference no greater than 3%).

Liver-Related Labs

Alkaline phosphatase elevations to at least two times the upper limit of normal occurred with higher incidence in donanemab-treated subjects compared to placebo in the placebo-controlled pool; however, the overall difference in donanemab vs placebo was small (0.6% versus 0.2%, respectively). This reviewer notes that a higher incidence of elevated alkaline phosphatase was not observed at baseline in the donanemab arm compared to placebo (donanemab arm: 7.1% [70/984]; placebo arm: 8.4% [84/999]). In most cases, the elevations occurred on multiple occasions. The following table shows incidences of subjects with maximum post-baseline liver enzyme values in the placebo-controlled pool.

Table 24. Maximum Post-Baseline for Liver Enzymes for the Placebo-Controlled Pool

Enzymes	Donanemab (N = 984)	Placebo (N = 999)
ALT >= 3 ULN	3 (0.3)	4 (0.4)
ALT >= 5 ULN	0 (0.0)	2 (0.2)
ALT >= 10 ULN	0 (0.0)	0 (0.0)
AST >= 3 ULN	2 (0.2)	2 (0.2)
AST >= 5 ULN	1 (0.1)	0 (0.0)
AST >= 10 ULN	0 (0.0)	0 (0.0)
BILI >= 2 ULN	3 (0.3)	4 (0.4)
ALP >= 2 ULN	6 (0.6)	2 (0.2)

This table was created by Senior Clinical Analyst Dr. Rui Li.

Similar incidences of maximum post-baseline liver enzyme values were observed in the all-donanemab pool compared to placebo (difference no greater than 0.2%).

Table 25. Maximum Post-Baseline for Liver Enzymes for the All-Donanemab Pool

Enzymes	Donanemab (N =2802)
ALT >= 3 ULN	6 (0.2)
ALT >= 5 ULN	2 (0.1)
ALT >= 10 ULN	0 (0.0)
AST >= 3 ULN	5 (0.2)
AST >= 5 ULN	1 (0.0)
AST >= 10 ULN	0 (0.0)
BILI >= 2 ULN	4 (0.1)
ALP >= 2 ULN	13 (0.5)

This table was created by Senior Clinical Analyst Dr. Rui Li.

The incidence of TEAEs related to the liver were similar in donanemab and placebo treated subjects in the placebo-controlled pool (1.6% versus 1.2%, respectively) and were consistent with the laboratory findings. The following table shows TEAEs belonging to the SOC of Investigations and related to the liver in the placebo-controlled pool.

Table 26. TEAEs Related to Liver in the Placebo-Controlled Pool

Preferred Term	Donanemab N=984 n (%)	Placebo N=999 n (%)
Subjects with TEAEs Belonging to SOC of Investigations Related to Liver Labs	16 (1.6)	12 (1.2)
Blood alkaline phosphatase increased	6 (0.6)	3 (0.3)
Gamma-glutamyltransferase increased	5 (0.5)	3 (0.3)
Blood bilirubin increased	3 (0.3)	1 (0.1)
Alanine aminotransferase increased	4 (0.4)	3 (0.3)
Liver function test increased	1 (0.1)	0
Aspartate aminotransferase increased	3 (0.3)	3 (0.3)
Transaminases increased	0	1 (0.1)
Hepatic enzyme increased	1 (0.1)	3 (0.3)

The reviewer created this using the IDB ADAE dataset, AESOC = Investigations. Submitted in the 90-Day Safety Update on September 11, 2023.

This reviewer did not identify any cases that met Hy's law criteria (alanine aminotransferase [ALT] or aspartate aminotransferase [AST] $\geq$ 3 ULN with a total bilirubin [TBILI] > 2 ULN and absence of alkaline phosphatase elevation at the time of bilirubin elevation).

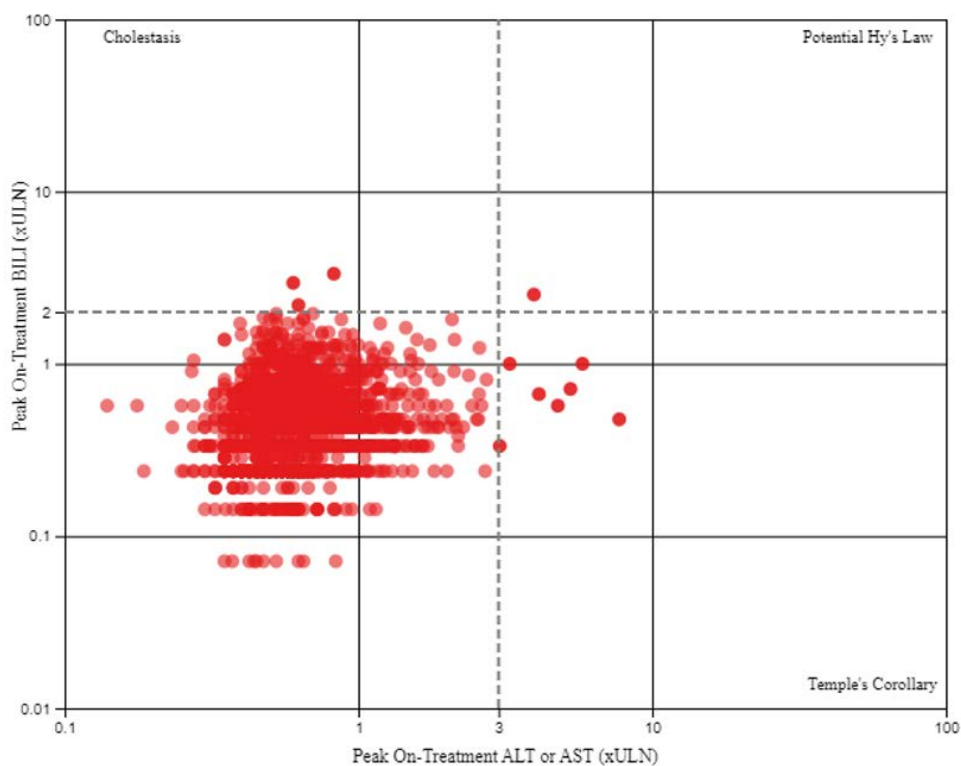
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In the all-donanemab pool, one subject (I5T-MC-AACI- (b) (6)) had alanine aminotransferase [ALT] and aspartate aminotransferase [AST] ≥ 3 ULN and total bilirubin [TBILI] > 2 ULN with alkaline phosphatase elevation ≥ 2 ULN at the time of bilirubin elevation).

In the all-donanemab pool, seven subjects on donanemab met Temple's Corollary (ALT and/or AST $\geq 3 \times$ ULN, without accompanying total bilirubin elevation),³⁵ indicating potential drug induced liver injury. In a review of narratives of these subjects, this reviewer was unable to establish a role for donanemab in the cases. Narratives of these cases are [below](#).

The following figure shows maximum total bilirubin by maximum ALT or AST in the all-donanemab pool at the 90-Day Safety Update.

Figure 4. Plot of Maximum Total Bilirubin versus Maximum ALT or AST in the All-Donanemab Pool at the 90-Day Safety Update.



The above figure was created by Senior Clinical Analyst Dr. Rui Li (email 12.8.23)

Narratives of Cases of Liver-Related Labs

³⁵ Noted in email communication dated November 22, 2023, with Senior Analyst Rui Li: I5T-MC-AACG- (b) (6) I5T-MC-AACI- (b) (6) I5T-MC-AACI- (b) (6) I5T-MC-AACI- (b) (6) I5T-MC-AAC (b) (6), and I5T-MC-AACI- (b) (6) and I5T-MC-AACI- (b) (6)

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In the all-donanemab pool, this reviewer summarizes one case with alanine aminotransferase [ALT] and aspartate aminotransferase [AST] ≥ 3 ULN, total bilirubin [TBILI] > 2 ULN, and concurrent alkaline phosphatase $> 2X$ ULN. The case, that appears to be cholestatic liver injury, is summarized here.

I5T-MC-AACI- (b) (6)

A 70-year-old male with past medical history of cholelithiasis and cholecystectomy (> 10 years prior to start of study), hypertension, increased GGT since screening ($> 3x$ ULN), normal BMI, alcohol use (5 units every week), not an active tobacco user, who was noted one month after the 7th dose of donanemab to have elevated ALT (4 x ULN), AST ($> 3 X$ ULN), total bilirubin (2.5 x ULN), alkaline phosphatase ((2.2 X ULN), and GGT (> 10 times the ULN) on Study Day 371. The subject was reported to have been asymptomatic. The prothrombin time was noted to be elevated on Study Days 386 and 491 (15.1 and 39.5 sec, respectively, with a reference range of reference range 9.7 to 12.3 sec). On Study Day 565, imaging of the liver (type not reported) showed scattered small non-shadowing echogenic foci in the liver, possibly granulomas. By Study Day 574, ALT, AST, total bilirubin, alkaline phosphatase, and prothrombin time had returned to normal levels. Donanemab treatment had not been restarted by the time of the data cutoff.

Between Study Days 386 to 511, the subject had negative tests for antinuclear antibody, hepatitis A virus antibody, hepatitis B surface antigen, antibody, and core antibody, hepatitis C antibody, hepatitis E virus IgG and IgM, hepatitis E virus IgG and IgM antibody ELISA, smooth muscle antibody, and normal values for platelet counts and hematocrit. F-actin smooth muscle antibody IgG (U) was within the normal reference range throughout the study (values ranged between 6 to 9 U from Study Day 386 to 511, with normal reference range of 19 U or less).^{36,37} The CPK levels remained within reference range throughout the study.

During the study, the subject reported AEs of ARIA-E and ARIA-H on Study Day 72 and ARIA-E on Study Day 168, 287, and 365 (all of mild severity). Treatment was interrupted because of the ARIA events. Concomitant medications included omeprazole, azilsartan, acetylsalicylic acid, citalopram, sildenafil, memantine, and Centrum Silver. No new medications had been started in the preceding 6 months before the event.

Reviewer comment: The subject was noted to have elevations in ALT, AST, alkaline phosphatase, total bilirubin, without a clear explanation for the elevation, which could be consistent with possible drug-induced liver injury. The pattern of liver injury is cholestatic based on an R-ratio of < 2 (R ratio for the case of 1.78 based on ALT: $3.96 x$ ULN/ALK PHOS: $2.22 x$ ULN). Although a

³⁶ Reference range for F-Actin (Smooth Muscle) Ab, IgG provided (b) (4) at [https://\(b\) \(4\) accessed on November 8, 2023.](https://(b) (4) accessed on November 8, 2023.)

³⁷ See patient profile for I5T-MC-AACI- (b) (6) starting on page 205 of the RSUR submitted June 12, 2023.

role for donanemab in the case could not be excluded, potential confounding factors existed including concomitant use of sildenafil, which has been associated with a cholestatic pattern of liver injury with apparent longer latency because of intermittent drug usage.³⁸ Other risk factors for the elevations include the subject's history of cholelithiasis, although the subject was noted to have undergone cholecystectomy > 10 years prior at the time of the cholelithiasis. The significance of isolated GGT elevation at baseline is unknown. This reviewer did not identify an etiology for the elevated baseline GGT, except for the subject's consumption of alcohol.

Subjects with ALT or AST > or = 3 Times the ULN

Per analyses by Dr. Rui Li, eight subjects had either ALT or AST $\geq$ 3 times the upper limit of normal in the all-donanemab pool, including one subject with elevated bilirubin > 2 times the upper limit of normal. This case is discussed above (I5T-MC-AACI-^{(b) (6)}). The remaining seven cases are summarized here.

In one case, this reviewer did not establish a role for donanemab because of a lack of workup to evaluate alternate causes for the liver enzyme elevation (I5T-MC-AACG-^{(b) (6)}). In this case, the subject experienced isolated elevation to the ALT (ALT value of 106 U/L, with an upper limit of normal of 35 U/L noted on Study Day 253) 49 days after the fifth dose of donanemab. The subject discontinued from treatment and the study due to the development of an AE of infusion related reaction on the same day as the 5th infusion (symptoms of chest tightness, flushing, and headache). The subject did not undergo additional evaluation for other causes of ALT elevation including infection or autoimmune cases. No concomitant medications had been started within 6 months of the elevated ALT.

This reviewer notes that in the six remaining cases, a role for donanemab was unlikely. In three cases, liver enzyme elevation occurred at a timeframe of ~ 6 months or greater since the last donanemab dose (I5T-MC-AACI-^{(b) (6)}, I5T-MC-AACI-^{(b) (6)}, I5T-MC-AACI-^{(b) (6)}). In one case, the liver enzyme elevation preceded the first dose of donanemab (I5T-MC-AACI-^{(b) (6)}). In another case, a role for donanemab could not be established as the elevation occurred after approximately 18 months of treatment (I5T-MC-AACI-^{(b) (6)}). In the remaining case, liver enzymes started to decline despite receiving additional dosing with donanemab (I5T-MC-AACI-^{(b) (6)}).

Subjects with Bilirubin > or = 2 Times the ULN

Per analyses by Dr. Rui Li, four subjects had bilirubin levels $\geq$ 2 times the upper limit of normal in the all-donanemab pool.

³⁸ Sildenafil. LiverTox. Clinical and Research Information on Drug-Induced Liver Injury [Internet]. <https://www.ncbi.nlm.nih.gov> Updated August 2, 2017. Accessed December 12, 2023.

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One of the four cases is discussed above ([I5T-MC-AACI-](#)(b) (6)).

In the remaining three cases, a role for donanemab could not be established as all subjects had bilirubin elevation prior to dosing with donanemab and at all postbaseline visits (I5T-MC-AACI-(b) (6) I5T-MC-AACI-(b) (6) and I5T-MC-AACI-(b) (6)).

Subjects with > or 2 Times the Upper Limit of Normal of Alkaline Phosphatase

Per analyses by Dr. Rui Li, 13 subjects had alkaline phosphatase levels ≥ 2 times the upper limit of normal in the all-donanemab pool.

One of the 13 cases is discussed above ([I5T-MC-AACI-](#)(b) (6)).

This reviewer did not establish a role for donanemab in the remaining 12 cases. In one case, this reviewer noted that the maximum alkaline phosphatase value occurred prior to dosing with donanemab (I5T-MC-(b) (6)). Four of the 12 cases had more than 5 months between the last dose of donanemab received and maximum alkaline phosphatase value (I5T-MC-AACI-(b) (6) I5T-MC-AACI-(b) (6) I5T-MC-AACI-(b) (6) and I5T-MC-AACI-(b) (6)). Four of the 12 cases had alkaline phosphatase elevation at screening or baseline visits and throughout the study (I5T-MC-AACI-(b) (6) I5T-MC-AACI-(b) (6) I5T-MC-AACI-(b) (6) and I5T-MC-AACI-(b) (6)). In two of the 12 cases, a role for donanemab was unlikely as went on to receive additional doses of donanemab and alkaline phosphatase levels remained in the normal range (I5T-MC-AACI-(b) (6) and I5T-MC-AACI-(b) (6)). In the remaining case, a role for donanemab could not be established as the alkaline phosphatase elevation occurred 16 days after the subject fell and fractured a clavicle (I5T-MC-AACI-(b) (6)).

Other Cases with Liver Enzyme Elevation

One subject in the all-donanemab pool reported a TEAE belonging to the SOC of Investigations related to liver enzyme elevation that was reported to lead to study withdrawal (hepatic enzyme increase, I5T-MC-AACI-(b) (6)). In this case, this reviewer did not identify a role for donanemab because the liver function tests were reported to have normalized despite receiving additional doses of donanemab.³⁹

Other Lab Findings

A review of mean change from baseline, shift to high, shift to low, shift from normal to abnormal, or CTCAE shifts to higher grades for chemistry or hematology laboratory results from the placebo-controlled pool did not identify a safety signal given small magnitudes of mean change from baseline. Similar findings were observed for the all-donanemab pool.

³⁹ Noted in the CIOMS form submitted in the Table of Significant and Notable patients submitted June 12, 2023.

The reader is referred to the [Appendix](#) for shift tables for the following lab parameters: glucose, creatine kinase, leukocytes, lymphocytes, and neutrophils.

8.4.7. Vital Signs

A review of mean change from baseline for vital signs, shift analyses for vital signs, and TEAEs related to vital signs and belonging to the SOC of Investigations did not identify a safety signal for vital signs.

This reviewer did not identify a safety signal in a review of mean change from baseline for vital signs because of small magnitudes of difference in the placebo-controlled pool and the all-donanemab pool.

A similar incidence of subjects in the donanemab and placebo arms had shift to abnormal vital signs in the placebo-controlled pool (difference no greater than 3%). The following table shows shifts in vital signs in the placebo-controlled pool.

Table 27.Shifts in Vital Signs in the Placebo-controlled Pool

Parameters	Donanemab (N = 984)	Placebo3 (N = 999)
Sitting Systolic Blood Pressure < 90 mm Hg	18 / 976 (1.8)	22 / 987 (2.2)
Sitting Systolic Blood Pressure > 140 mm Hg	261 / 507 (51.5)	272 / 521 (52.2)
Sitting Systolic Blood Pressure > 160 mm Hg	40 / 507 (7.9)	46 / 521 (8.8)
Orthostatic Change (Supine to Standing) in Systolic Blood Pressure > 20 mm Hg	111 / 869 (12.8)	119 / 901 (13.2)
Sitting Diastolic Blood Pressure < 50 mm Hg	39 / 975 (4.0)	39 / 988 (3.9)
Sitting Diastolic Blood Pressure > 90 mm Hg	176 / 903 (19.5)	197 / 896 (22.0)
Sitting Diastolic Blood Pressure > 100 mm Hg	15 / 903 (1.7)	21 / 896 (2.3)
Orthostatic Change (Supine to Standing) in Diastolic Blood Pressure > 10 mm Hg	143 / 857 (16.7)	158 / 902 (17.5)
Sitting Pulse < 60 bpm	254 / 541 (47.0)	250 / 533 (46.9)
Sitting Pulse > 100 bpm	13 / 972 (1.3)	22 / 987 (2.2)
Orthostatic Change (Supine to Standing) in Pulse > 30 bpm	12 / 907 (1.3)	19 / 933 (2.0)

Parameters	Donanemab (N = 984)	Placebo3 (N = 999)
Temperature < 36.0 C	215 / 882 (24.4)	216 / 896 (24.1)
Temperature > 38.0 C	6 / 977 (0.6)	10 / 991 (1.0)
Decrease Weight > 7%	120 / 949 (12.6)	118 / 969 (12.2)
Increase Weight > 7%	103 / 949 (10.9)	114 / 969 (11.8)

This table was created by Senior Clinical Analyst Dr. Rui Li.

A similar incidence of subjects in the all-donanemab pool had shift to abnormal compared to placebo (difference no higher than 4%) except for sitting pulse < 60 beats per minute, where a lower incidence was observed in the all-donanemab pool (38.5% versus 47%, respectively).

TEAEs Related to Vital Sign Parameters

A review of TEAEs related to vital sign findings showed similar incidences between donanemab and placebo arms in the placebo-controlled pool (difference no greater than 0.6%). A similar incidence of TEAEs related to vital sign findings was observed in the all-donanemab pool compared to placebo (difference no greater than 1%).

The reviewer is referred to the [Hypersensitivity and Infusion Related Reactions](#) section for further details regarding increases and decreases in blood pressure and increases in heart rate at the time of infusion or within minutes following the end of the infusion.

8.4.8. Electrocardiograms (ECGs)

This reviewer did not identify a safety signal in an analysis of mean change from baseline, shift to abnormal, and TEAEs related to electrocardiograms (ECGs).

The reader is referred to the [Routine Clinical Tests](#) section of this review for methods of ECG collection and ECG reading, and to the [Appendix](#) for the number of subjects who contributed to each timepoint when ECGs were performed.

The Applicant analyzed mean change from baseline and shift analyses for mean heart rate, PR interval, QRS interval, and QT interval corrected by Fridericia (QTcF) for evaluation of changes in ECGs associated with donanemab therapy in Studies AACG, AACH, and AACI. Study AACN-Dona cohort did not contribute to ECG analyses, as post-baseline ECGs were not collected.

This reviewer did not identify a safety signal for ECG parameters in analyses of mean change from baseline for heart rate, PR interval, QRS interval, and RR duration for the placebo-controlled pool or the all-donanemab pool because of small magnitudes of change.

Donanemab- and placebo-treated subjects had similar incidences of shift to abnormal for ECG parameters in the placebo-controlled pool (difference no greater than 1%). The following table shows shift to abnormal for ECG parameters in the placebo-controlled pool.

Table 28. Shift to Abnormal for ECG Parameters in Subjects with Baseline ECGs in the Placebo-controlled Pool.

Parameters	Donanemab (N = 981)	Placebo (N = 998)
Heart rate < 50 bpm	181 (18.5)	190 (19.0)
Heart rate > 100 bpm	7 (0.7)	7 (0.7)
PR interval < 120 msec	12 (1.2)	16 (1.6)
PR interval >= 220 msec	95 (9.7)	90 (9.0)
QRS < 60 msec	0 (0.0)	0 (0.0)
QRS > 120 msec	99 (10.1)	81 (8.1)

This table was created by Senior Clinical Analyst Dr. Rui Li.

In the all-donanemab pool, subjects had lower incidences of shift to abnormal for ecg parameters compared to donanemab-treated subjects in the placebo-controlled pool. The lower incidences maybe due to selection bias as subjects who continued to receive donanemab in the all-donanemab pool may have been less likely to experience adverse events compared to donanemab-treated subjects who experienced adverse events and did not continue with donanemab treatment.

The reader is referred to the following section for analyses of the QT interval.

TEAEs Related to ECG Parameters

Donanemab- and placebo-treated subjects had similar incidences of reporting TEAEs related to ECG abnormalities in the placebo-controlled pool (difference no greater than 0.2%). Subjects in the all-donanemab pool had similar incidences of reporting TEAEs related to abnormal ECG parameters compared to the placebo-controlled pool (difference no greater than 0.1%).

Three SAEs of sinus node dysfunction were reported in the all-donanemab pool with verbatim term of sick sinus syndrome. Two of the SAEs of sinus node dysfunction were reported in donanemab-treated subjects in the placebo-controlled pool compared to none on placebo (0.2% versus none, respectively). In all three cases, this reviewer did not establish a role for donanemab because of presence of risk factors including history of atrial fibrillation and

bradycardia. The reader is referred to the [SAEs section](#) of this review for a review of these cases (I5T-MC-AACG- (b) (6) I5T-MC-AACI- (b) (6) and I5T-MC-AACI- (b) (6)).

8.4.9. QT

This reviewer did not identify a safety signal in an analysis of mean change from baseline, shift to QTcF intervals > 450, 480, and 500 msec, and TEAEs related to abnormal QT interval in the placebo-controlled or all-donanemab pool.

No adverse events of torsades were reported in Phase 1 studies or the all-donanemab pool.

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

This reviewer did not identify a safety signal in analyses of mean change from baseline for QT interval and QTcF interval for the placebo-controlled pool or the all-donanemab pool because of small magnitudes of change from baseline.

Donanemab-treated subjects were not observed to have higher incidences of shifts in QT interval using Fridericia's Correction (QTcF) compared to placebo in the placebo-controlled pool. The following table shows shift to abnormal for ECG parameters in the placebo-controlled pool.

Table 29. Shift in QTcF in Subjects with Baseline ECGs in the Placebo-controlled Pool.

Parameters	Donanemab (N = 981)	Placebo (N = 998)
QTcF > 450 msec	85 (8.7)	92 (9.2)
QTcF > 480 msec	12 (1.2)	12 (1.2)
QTcF > 500 msec	1 (0.1)	4 (0.4)

This table was created by Senior Clinical Analyst Dr. Rui Li.

TEAEs Related to Prolonged QT Interval

Donanemab-treated subjects did not report a higher incidence of TEAEs related to prolonged QT interval compared to placebo in the placebo-controlled pool (0.4% versus 0.6%, respectively).

Subjects in the all-donanemab pool did not have a higher incidence of reporting TEAEs related to prolonged QT interval compared to the placebo-controlled pool.

No TEAEs of Torsades were reported. One TEAE of ventricular fibrillation was reported in one-donanemab-treated subject (15T-MC-AACI-^{(b) (6)}). The subject also experienced SAEs of cardiac arrest and had a history of coronary artery disease as a likely predisposing risk factor. The case is discussed further in the SAEs section of this review.

8.5. Analysis of Submission-Specific Safety Issues

8.5.1. Immunogenicity

The protocol for sampling for immunogenicity of donanemab and definitions of treatment emergent antidrug-antibody (ADA) and neutralizing antibodies is included in the [Appendix](#).

Reviewer comment: The Guidance for Industry: Immunogenicity Testing of Therapeutic Protein Products —Developing and Validating Assays for Anti-Drug Antibody Detection (January 2019) recommends obtaining pre-treatment samples, samples at multiple intervals throughout the trial, and samples at approximately five half-lives after last exposure (~60 days given donanemab's half-life of ~12 days as noted in the Applicant's Clinical Overview). Overall, this reviewer finds the Applicant's sampling strategy to be acceptable.

In up to 18 months of treatment in the placebo-controlled period of AACI, 87.2% (691/792) of donanemab-treated subjects had treatment-emergent ADA positive status compared to 5.8% (48/821) on placebo. All (691/691) were positive for neutralizing antibodies.

In the placebo-controlled pool and the all-donanemab pool, similar findings were observed. In up to 18 months of treatment in the placebo-controlled pool, 87.9% (810/921) of donanemab-treated subjects had treatment-emergent ADA positive status compared to 5.6% (53/944) on placebo. In the all-donanemab pool, 88.1% of subjects had treatment-emergent ADA positive status. In both pools, all subjects with treatment-emergent ADA positive status had neutralizing antibodies. The reader is referred to the [Appendix](#) for tables of the incidence of subjects with treatment-emergent ADA in the placebo-controlled period of AACI, the placebo-controlled pool, and the all-donanemab pool.

The incidence of infusion related reactions was higher in donanemab-treated subjects with TE ADA positive status compared to those with TE ADA negative status in the placebo-controlled period of AACI (9.8% versus 2.0%, respectively). The following table shows the incidence of infusion related reaction by TE ADA status in the placebo-controlled period of AACI.

Table 30. Infusion Related Reaction by Treatment Emergent ADA Status in the Placebo-Controlled Period of AACI

Preferred Term	Donanemab		Placebo	
	TE ADA Positive N=691 n (%)	TE ADA Negative N=101 n (%)	TE ADA Positive N=48 n (%)	TE ADA negative N=773 n (%)
Infusion Related Reaction	68 (9.8)	2 (2.0)	0	3 (0.4)

The reviewer created this using the IDB ADIS and ADAE dataset submitted in the 90-Day Safety Update on September 11, 2023.

8.5.2. ARIA and Intracerebral Hemorrhage

Monoclonal antibodies directed against aggregated forms of beta amyloid, can cause ARIA, characterized as ARIA with edema (ARIA-E), observed on MRI as brain edema or sulcal effusions, and ARIA with hemosiderin deposition (ARIA-H), which includes microhemorrhage and superficial siderosis. ARIA-H can occur spontaneously in people with Alzheimer's disease. ARIA-H of any cause and ARIA-E may occur in isolation or together; ARIA-H associated with monoclonal antibodies directed against aggregated forms of beta amyloid generally occurs in association with an occurrence of ARIA-E. The following section focuses on findings of ARIA and intracerebral hemorrhage observed in donanemab clinical trials.

The reader is referred to the [Appendix](#) for definitions and management of ARIA.

Methods

ARIA events were recorded as adverse events and as MRI findings AACG and AACI. ARIA-E findings were required to be reported as adverse events by investigators, but this was not specified for ARIA-H events. Symptoms associated with ARIA-E, seriousness of ARIA events, and ARIA events reported to lead to study withdrawal and treatment discontinuation were recorded in the adverse event dataset.⁴⁰ Given that the different datasets recorded different information, analyses in this section of the review will specify whether the analysis was based on the adverse event dataset or the MRI dataset.

Reviewer comment: In estimating the incidence of ARIA-H, this reviewer considered the dataset containing MRI findings to be the more comprehensive dataset for ARIA findings, in agreement with the applicant's approach. This reviewer considered the adverse event dataset to be the

⁴⁰ Input for the MRI dataset was based on information collected from MRI worksheets. A sample MRI Brain Worksheet from Study AACI was included in the Applicant's response dated October 3, 2023, to an information request dated October 2, 2023.

more comprehensive dataset for clinical symptoms associated with ARIA, seriousness, and whether events were reported to lead to study withdrawal and treatment discontinuation.

Incidence of ARIA and Intracerebral Hemorrhage > 1 cm

Analyses of clinical outcomes of ARIA events, occurring within 57 days of a dose of donanemab, are based on adverse events recorded in the ADAE dataset. Analyses of the incidence of ARIA are based on the MRI dataset and are indicated by footnotes within the tables.

Clinical outcomes of ARIA events such as fatality, seriousness, or event reported to lead to study withdrawal or treatment discontinuation were recorded in the adverse event dataset; therefore, this reviewer considered the adverse event dataset, rather than the MRI dataset, to be the more comprehensive source for these events.

Consistent with the findings from other monoclonal antibodies directed against aggregated forms of beta amyloid, donanemab can cause ARIA, including ARIA-E and ARIA-H. The table below shows the incidence of ARIA or intracerebral hemorrhage > 1 cm within 57 days of a dose of donanemab in the placebo-controlled period of AACI.

Table 31. Incidence of Treatment Emergent ARIA or Intracerebral Hemorrhage > 1 Cm in the Placebo-controlled Period of AACI^a

Event	Donanemab N=853 n (%)	Placebo N=874 n (%)
ARIA	307 (36.0)	122 (14.0)
ARIA-E	201 (23.6)	17 (1.9)
Isolated ARIA-E	44 (5.2)	11 (1.3)
Symptomatic ARIA-E ^b	52 (6.1)	0
ARIA-H	263 (30.8)	111 (12.7)
Isolated ARIA-H	106 (12.4)	105 (12.0)
ARIA-H microhemorrhage	217 (25.4)	100 (11.4)
ARIA-H superficial siderosis	125 (14.7)	23 (2.6)
Intracerebral Hemorrhage > 1 cm ^c	4 (0.5)	2 (0.2)

^aThe 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.

^bSymptoms of ARIA-H were not collected in Study AACI. The incidence of symptomatic ARIA-E is based on the adverse event dataset.

^cThe donanemab arm includes three subjects identified from the MRI dataset: I5T-MC-AACI- (b) (6), I5T-MC-AACI- (b) (6), and I5T-MC-AACI- (b) (6); and one subject from the adverse event dataset: I5T-MC-AACI- (b) (6) (based on a review of the narrative). The placebo arm includes two subjects identified from the MRI dataset: I5T-MC-AACI- (b) (6) and I5T-MC-AACI- (b) (6).

The reader is referred to the Appendix for [tables](#) of the incidence of isolated ARIA in the

placebo-controlled period of AACI and the placebo-controlled pool and for a [table](#) of subjects with intracerebral hemorrhage > 1 cm in the placebo-controlled pool.

The incidence of ARIA in the all-donanemab pool is shown in the following table. In that pool, intracerebral hemorrhage > 1 cm occurred in 0.3% (8/2802) of donanemab-treated subjects. The incidence of ARIA in the 1818 subjects in the all-donanemab pool who had not received donanemab in Study AACG or the placebo-controlled period of AACI was similar to that in the all-donanemab pool overall. The reader is referred to the [Appendix](#) for the incidence of ARIA in subjects in the all-donanemab pool who had not received donanemab in Study AACG or the placebo-controlled period of AACI.

Table 32. Incidence of ARIA or Intracerebral Hemorrhage > 1 cm in the All-Donanemab Pool^a

	Donanemab (N =2802)
ARIA	882 (31.5%)
ARIA-E	562 (20.1%)
Isolated ARIA-E	140 (5.0%)
Symptomatic ARIA-E ^b	126 (4.5%)
ARIA-H	742 (26.5%)
Isolated ARIA-H	320 (11.4%)
ARIA-H, Microhemorrhages	610 (21.8%)
ARIA-H, Superficial Siderosis	330 (11.8%)
Intracerebral hemorrhage > 1 cm ^c	8 (0.3)

^aThe incidence of ARIA is based on analyses using the MRI dataset provided by Senior Clinical Analyst Dr. Rui Li. The incidence of intracerebral hemorrhage > 1 cm is based on analyses using the combined adverse event, MRI datasets, and a review of narratives.

^bSymptoms of ARIA-H were not collected in Study AACI. The incidence of symptomatic ARIA-E is based on the adverse event dataset.

^cThis does not include IST-MC-AACI- (b) (6) with an event that started > 57 days from the last dose.

The incidences of SAEs and discontinuations attributed to ARIA in the placebo-controlled period of AACI were higher in the donanemab arm compared to placebo as shown in the following table, with similar findings in the placebo-controlled pool (tables in [SAEs](#), [treatment discontinuations](#), and [TEAEs](#) sections) and in the all-donanemab pool (tables in the [SAEs](#), [treatment discontinuations](#), and [TEAEs](#) section). Treatment discontinuation was driven in part

by protocol-specified discontinuation criteria. Treatment was reported to have been interrupted in the majority of donanemab-treated subjects who developed ARIA-E in the placebo-controlled pool (144/201, 72%), and withdrawn in 10% (21/201). The reader is referred to the [Appendix](#) for treatment discontinuation parameters related to ARIA in the placebo-controlled period of AACI.

Table 33. SAEs and Treatment Discontinuations Associated with ARIA in the Placebo-Controlled Period of AACI

	Donanemab N=853 n (%)	Placebo N=874 n (%)
SAEs	14 (1.6)	0
Treatment Discontinuations	29 (3.4)	5 (0.6)

This reviewer created this table using analyses of the adverse event dataset.

As discussed in Section 8.4.1 of this review, two deaths were associated with ARIA-E and/or ARIA-H and 1 death was caused by intracerebral hemorrhage in the setting of ARIA-H in the donanemab arm of the placebo-controlled period of AACI, with an additional death due to ARIA-E in the all-donanemab pool and an additional death due to intracerebral hemorrhage in the all-donanemab pool in a subject who received thrombolytic therapy in the setting of ARIA-E.

Clinical Symptoms Associated with ARIA-E

The incidence of symptomatic ARIA noted in labeling is based on the incidence of symptomatic ARIA-E because symptoms of ARIA-H were not collected in Studies AACG, AACH, and AACI.

The majority of ARIA-E cases in the placebo-controlled period of AACI were asymptomatic. Symptomatic ARIA-E occurred in 6.1% [52/853] of donanemab-treated subjects in the placebo-controlled period of AACI compared to none (0/874) on placebo.

In the placebo-controlled period of AACI, severe symptoms of ARIA-E were reported in 1.2% (10/853), moderate in 1.4% (12/853), and mild in 3.5% (30/853) of donanemab-treated subjects. The symptoms that were associated with ARIA-E were not categorized as serious or non-serious in the trial.

Clinical symptoms of ARIA-E resolved in 84.6% (44/52) of donanemab-treated subjects in the placebo-controlled period of AACI.

In the placebo-controlled period of AACI, the most frequent symptoms reported with ARIA-E were headache, confusion, dizziness, nausea, and seizure. Seizure as a symptom of ARIA-E was

reported in 0.6% of donanemab-treated subjects in the placebo-controlled period of AACI. Among subjects with ARIA in the placebo-controlled period of AACI, the incidence of seizure was 2% (5/307) among donanemab-treated subjects compared to none on placebo (0/122). The reader is referred to the [Appendix](#) for symptoms reported with ARIA-E and severity of those symptoms in the placebo-controlled period of AACI and the placebo-controlled pool.

In the all-donanemab pool, the incidence of symptomatic ARIA-E was similar to that in the placebo-controlled period of AACI (4.5% [126/2802] versus 6.1%, respectively). In the all-donanemab pool, headache, confusion, and dizziness were the most frequent symptoms reported. Seizure as a symptom of ARIA-E was reported in 0.2% of the all-donanemab pool.

The reader is referred to the [Appendix](#) for tables of ARIA events related to deaths, SAEs, study withdrawals, and treatment discontinuations in the placebo-controlled period of AACI and the placebo-controlled pool.

The Applicant conducted an analysis of subsequent ARIA events in subjects with symptomatic ARIA-E and maximum radiographic severity rating of mild who continued to receive treatment with donanemab. The Applicant identified 21 subjects with symptomatic ARIA-E and maximum radiographic severity of mild. Of these 21 subjects, 5 subjects continued to treatment with donanemab.⁴¹ Three of the five subjects had additional ARIA events.⁴² A conclusion regarding treatment through symptomatic ARIA-E in subjects with a maximum severity of mild ARIA cannot be drawn given the low number of subjects in this group.

Incidence of Intracerebral Hemorrhage > 1 cm

Analyses of intracerebral hemorrhage > 1 cm are based on a review of both the adverse event and the MRI datasets. This reviewer used the EMQ/FMQ grouping of Intracranial Hemorrhage to identify events of intracerebral hemorrhage >1 cm within the adverse event dataset. For additional analyses of TEAEs belonging to this grouping, the reader is referred to the [Appendix](#).

In analyses based on the MRI and adverse event datasets, intracerebral hemorrhage greater than 1 cm occurring within 57 days after the last dose of study drug was reported in 0.5% (4/853) of subjects on donanemab and in 0.2% (2/874) subjects on placebo in the placebo-controlled period of AACI. Intracerebral hemorrhage greater than 1 cm occurred in 0.3% (8/2802) in the all-donanemab pool.

⁴¹ Noted in the Applicant's response dated January 12, 2024, to an information request dated January 10, 2024. Participants: I5T-AACI- (b) (6) (also in the placebo-controlled period of AACI), I5T-AACI- (b) (6) (also in the placebo-controlled period of AACI), I5T-AACI- (b) (6), I5T-AACI- (b) (6), and I5T-AACI- (b) (6).

⁴² AACI- (b) (6) (one ARIA-H event), AACI- (b) (6) (one additional ARIA-E event and two ARIA-H events) and AACI- (b) (6) (two additional ARIA-E events and four ARIA-H events).

In a review of these subjects' past medical history, concomitant medications, blood pressures at study visits, and ApoE ϵ 4 status, this reviewer notes all had at least one of the following as a risk factor for intracerebral hemorrhage: antithrombotic or thrombolytic use, elevated blood pressure or diagnosis of hypertension, and ApoE ϵ 4 allele.⁴³ Additionally, this reviewer notes these subjects had screening MRI findings of white matter disease changes, superficial siderosis, and microhemorrhages, which are findings seen in people with cerebral amyloid angiopathy, and cerebral amyloid angiopathy is a risk factor for intracerebral hemorrhage.⁴⁴ The following table identifies subjects in the all-donanemab pool with intracerebral hemorrhage > 1 cm within 57 days after the last dose of donanemab.

Table 34. Subjects with Intracerebral Hemorrhage > 1 cm in the All-Donanemab Pool.

USUBJID Study	Event of Intracerebral Hemorrhage	Risk Factors	Abnormal Screening MRI Findings Postbaseline ARIA Events ^a	Comments
I5T-MC- AACI- (b) (6) (b) (6) LTE of AACI	Intracerebral Hemorrhage	• ϵ3/ϵ4 • CM: Tenecteplase 22 mg once	• Screening MRI: Focal lesions of white matter disease • Postbaseline ARIA events: ARIA-E and ARIA-H SS (70 mm)	Fatal Case Occurred in the setting of thrombolytic therapy and ARIA-E
I5T-MC- AACI- (b) (6) (b) (6) AACI Safety Addendum	Intracerebral hemorrhage	• ϵ3/ϵ4 • PMH: HTN • CM: ASA 81 mg daily	• Screening MRI: Focal lesions of white matter disease • Postbaseline ARIA events: ARIA-E, ARIA-H Mh (1), and ARIA-H SS (20 mm)	ARIA-E, ARIA-H Mh (1) and SS (20 mm) on SD 71 in same location as intracerebral hemorrhage on SD 99.
I5T-MC- AACI- (b) (6) (b) (6) PC of AACI	Intracerebral hemorrhage	• ϵ3/ϵ4 • CM: Prasugrel 10 mg daily	• Screening MRI: Focal lesions of white matter disease • Postbaseline ARIA events: ARIA-E, ARIA-H Mh (2) and ARIA-H SS (14 mm)	ARIA-E and SS on SD 74 in the same area of intracerebral hemorrhage on SD 192

⁴³Marini S, Crawford K, Morotti A, et al. Association of Apolipoprotein E With Intracerebral Hemorrhage Risk by Race/Ethnicity: A Meta-analysis JAMA Neurol. 2019 Apr 1;76(4):480-491. doi: 10.1001/jamaneurol.2018.4519.

⁴⁴Charidimou A, Boulouis G, Frosch M. The Boston criteria version 2.0 for cerebral amyloid angiopathy: a multicentre, retrospective, MRI-neuropathology diagnostic accuracy study. Lancet Neurol. 2022 Aug;21(8):714-725. doi: 10.1016/S1474-4422(22)00208-3.

USUBJID Study	Event of Intracerebral Hemorrhage	Risk Factors	Abnormal Screening MRI Findings Postbaseline ARIA Events ^a	Comments
I5T-MC- AACI- (b) (6) (b) (6) LTE of AACI	Intracerebral hemorrhage	• ε3/ε4	• Screening MRI: Focal lesions of white matter disease, one microhemorrhage	An MRI on SD 618 showed a 13 mm intracerebral hemorrhage in the right temporal lobe (3 days after the 3rd donanemab infusion). The subject was reported to have been asymptomatic and on SD 623, donanemab was discontinued. The mean blood pressure value in the 6 study visits in the preceding 6 months before the event of intracerebral hemorrhage was 119/76 mmHg (range: 114 to 124 /69 to 80 mmHg)
I5T-MC- AACI- (b) (6) (b) (6) AACI Safety Addendum	Intracerebral hemorrhage	• ε3/ε4 • PMH: HTN • Fall	• Screening MRI: Beginning of confluence of lesions of white matter disease • Postbaseline ARIA events: ARIA-E	Pt had an intracerebral hemorrhage of unidentified size (right occipital lobe, SD 74) within 57 days of the last dose of donanemab (in the adverse event dataset) and an intracerebral hemorrhage > 1 cm > 57 days from the last dose of donanemab (Study Day 130, MRI dataset, right occipital lobe). On SD 67, pt had ARIA-E (cerebellum and parietal

USUBJID Study	Event of Intracerebral Hemorrhage	Risk Factors	Abnormal Screening MRI Findings Postbaseline ARIA Events ^a	Comments
				lobes and right frontal lobe) and a lacunar infarct (right cerebellum)
I5T-MC-AACI- (b) (6) (b) (6) PC of AACI	Intracerebral hemorrhage	• ε3/ε4 • PMH: HTN	• Screening MRI: Focal lesions of white matter disease • Postbaseline ARIA events: ARIA-E, ARIA-H Mh (3), and ARIA-H SS (20 mm)	ARIA-E on SD 71 in the same location as intracerebral hemorrhage on SD 526. Also ARIA-E and 3 Mh in the same location as the intracerebral hemorrhage on SD 526.
I5T-MC-AACI- (b) (6) (b) (6) PC of AACI	Hemorrhagic stroke	• ε3/ε4 • Elevated blood pressure in study	• Screening MRI: Focal lesions of white matter disease, SS (25 mm)	Blood pressure at the two study visits preceding the event was 142/82 and 146/88 mmHg.
I5T-MC-AACI- (b) (6) (b) (6) PC of AACI	Severe intracerebral hemorrhage and hemorrhagic stroke with mass effect (Hematoma 5.5 x 4.3 cm)	• PMH: HTN • CM: Several acetylsalicylic acid tablets (amount not specified)	• Screening MRI: Beginning of confluence of lesions of white matter disease, SS (50 mm) • Postbaseline ARIA events: ARIA-E, ARIA-H Mh (1), and ARIA-H SS (65 mm)	Fatal Case where death certificate listed both ARIA-H and hemorrhagic stroke as the cause of death Had ARIA-E in the same location as hematoma. ARIA-E on SD 71 (included left parietal area). Hematoma (left parietal) noted on SD 72 based on review of the narrative, (5.5 x 4.3 cm)

CM: concomitant medication, HTN: hypertension, LTE: long-term extension period, Mh: microhemorrhage, PC: placebo-controlled period, PMH: past medical history, SAH: subarachnoid hemorrhage, SD: study day, SS: superficial siderosis

^aPostbaseline ARIA Events Prior to Intracerebral Hemorrhage and up to 30 Days After (identified using the MRI and adverse event datasets).

The reader is referred to the [Appendix](#) for a table of subjects with events of intracerebral hemorrhage > 1 cm (as noted above) as well as events of intracerebral hemorrhage where the size was unknown. The table also includes subjects with thalamus hemorrhage, subarachnoid hemorrhage, and cerebral hematoma.

Radiographic Severity of ARIA (MRI Dataset)

The reader is referred to the [Appendix](#) for MRI classification of ARIA events.

Reviewer comment: Overall, this reviewer found the Applicant's approach for MRI classification of ARIA to be acceptable.

Donanemab-treated subjects had higher incidences of radiographically severe ARIA-E, ARIA-H, ARIA-H Microhemorrhage, and ARIA-H Superficial Siderosis compared to subjects on placebo in the placebo-controlled period of AACI.

The following table shows maximum radiographic severity of ARIA in the placebo-controlled period of AACI. Similar findings of incidence of severe ARIA were observed in the placebo-controlled pool among donanemab-treated subjects. Similar incidences of radiographically severe ARIA were observed in the all-donanemab pool (difference no greater than 2%). The reader is referred to the [Appendix](#) for tables showing maximum radiographic severity of ARIA in the placebo-controlled pool and the all-donanemab pool.

Table 35. Maximum Radiographic Severity of ARIA in the Placebo-controlled Period of AACI (MRI dataset)^a

Preferred Terms	Severity	Donanemab (N = 853)	Placebo (N = 874)
Total Subjects with any ARIA (-E or H)	Questionable	0 (0.0%)	0 (0.0%)
	Mild	120 (14.1%)	100 (11.4%)
	Moderate	104 (12.2%)	19 (2.2%)
	Severe	83 (9.7%)	3 (0.3%)
	Total	307 (36.0%)	122 (14.0%)
ARIA-E	Questionable	0 (0.0%)	0 (0.0%)
	Mild	59 (6.9%)	14 (1.6%)
	Moderate	128 (15.0%)	3 (0.3%)
	Severe	14 (1.6%)	0 (0.0%)
	Total	201 (23.6%)	17 (1.9%)
ARIA-H	Questionable	0 (0.0%)	0 (0.0%)
	Mild	135 (15.8%)	92 (10.5%)
	Moderate	50 (5.9%)	16 (1.8%)
	Severe	78 (9.1%)	3 (0.3%)
	Total	263 (30.8%)	111 (12.7%)
ARIA-H, Microhemorrhages	Questionable	0 (0.0%)	0 (0.0%)
	Mild	143 (16.8%)	88 (10.1%)
	Moderate	34 (4.0%)	11 (1.3%)

Preferred Terms	Severity	Donanemab (N = 853)	Placebo (N = 874)
ARIA-H, Superficial Siderosis	Severe	40 (4.7%)	1 (0.1%)
	Total	217 (25.4%)	100 (11.4%)
	Questionable	0 (0.0%)	0 (0.0%)
	Mild	47 (5.5%)	16 (1.8%)
	Moderate	32 (3.8%)	5 (0.6%)
	Severe	46 (5.4%)	2 (0.2%)
	Total	125 (14.7%)	23 (2.6%)

This table was created by Senior Clinical Analyst Dr. Rui Li.

*Severity of events of intracerebral hemorrhage > 1 cm was not recorded in the MRI dataset.

Timing of ARIA – Onset and Duration (MRI Dataset)

Among donanemab-treated subjects who developed ARIA-E in the placebo-controlled period of AACI, approximately 58% developed ARIA-E before the fourth dose of donanemab and 89% of subjects before the 7th dose. ARIA-E was noted to occur as late as after the 19th dose in the placebo-controlled period of AACI.

Similar findings were observed for the all-donanemab pool after the first three and the first six doses (difference no greater than 5%).

The following table shows the number of doses donanemab-treated subjects received prior to developing the first episode of ARIA-E in the placebo-controlled period of AACI. Similar findings were observed for the placebo-controlled pool. The reader is referred to the [Appendix](#) for a table of ARIA-E by number of doses received for the placebo-controlled pool.

Table 36. Number of Doses Prior to First ARIA-E in Donanemab-Treated Subjects in the Placebo-controlled Period of AACI (MRI dataset).

Number of Dose Prior ARIA-E	First ARIA-E Subject Numbers	Cumulative First ARIA-E Subject Numbers N(%)
1	8	8 (4.0)
2	18	26 (12.9)
3	90	116 (57.7)
4	6	122 (60.7)
5	8	130 (64.7)
6	49	179 (89.1)
7	9	188 (93.5)
10	1	189 (94.0)
11	1	190 (94.5)
13	10	200 (99.5)
19	1	201 (100)

This table was created by Senior Clinical Analyst Dr. Rui Li.

Among donanemab-treated subjects who developed ARIA-H in the placebo-controlled period of AACI, approximately 41% of donanemab-treated subjects had developed ARIA-H before the fourth dose of donanemab and 71% of subjects before the seventh dose. ARIA-H was noted to

occur as late as after the 19th dose. Similar findings of the incidence of subjects with ARIA-H before the fourth and seventh doses were observed for the placebo-controlled pool and the all-donanemab pool (difference no greater than 10%).

The following table shows the number of doses donanemab-treated subjects received prior to developing ARIA-H in the placebo-controlled period of AACI. The reader is referred to the [Appendix](#) for the number of doses received prior to the development of ARIA-H for the placebo-controlled pool.

Table 37. Number of Doses Prior to ARIA-H in Donanemab-Treated Subjects in the Placebo-controlled Period of AACI (MRI dataset).

Number of Dose Prior ARIA-H	First ARIA-H Subject Numbers	Cumulative First ARIA-H Subject Numbers N(%)
1	6	6 (2.3)
2	11	17 (6.5)
3	92	109 (41.4)
4	4	113 (43.0)
5	8	121 (46.0)
6	66	187 (71.1)
7	14	201 (76.4)
8	3	204 (77.6)
9	1	205 (77.9)
11	4	209 (79.5)
12	5	214 (81.4)
13	30	244 (92.8)
14	4	248 (94.3)
16	1	249 (94.7)
17	1	250 (95.1)
19	13	263 (100)

This table was created by Senior Clinical Analyst Dr. Rui Li.

In the placebo-controlled period of AACI, the median time to first episode of ARIA-E in donanemab-treated subjects was 47 days (minimum: 9 days, maximum: 286 days).

Similar findings for median time to first episode of ARIA-E were observed for the placebo-controlled pool and the all-donanemab pool.

The reader is referred to the [Appendix](#) for tables on time to first episode of ARIA-E for the placebo-controlled period of AACI and the placebo-controlled pool.

In donanemab-treated subjects in the placebo-controlled period of AACI, 63% of subject's first ARIA-E event resolved by the 12th week and 80% by the 20th week.

Similar findings of time to resolution for the first ARIA-E event were observed for the placebo controlled pool (difference no greater than 1%) and the all-donanemab pool at 12 and 20 weeks (difference no greater than 6%).

The following table shows the time to resolution of the first event of ARIA-E for the pooled placebo-controlled period of AACI. The reader is referred to the [Appendix](#) for time to resolution of the first event of ARIA-E for the placebo-controlled pool.

Table 38. Time to Resolution of First Event of ARIA-E for the Placebo-controlled Period of AACI.

Time to Resolution	Donanemab (N = 201)		Placebo (N = 17)	
	No. of First ARIA-E Resolved	Cumulative First ARIA-E Resolved N(%)	No. of First ARIA-E Resolved	Cumulative First ARIA-E Resolved N(%)
<= 12 Weeks	126	126 (62.7)	6	6 (35.3)
<= 20 Weeks	34	160 (79.6)	1	7 (41.2)
End of Study	6	166 (82.6)	0	7 (41.2)

This table was created by Senior Clinical Analyst Dr. Rui Li using the ADTTE dataset.

Multiple Episodes of ARIA

Approximately 6.5% of donanemab-treated subjects who developed ARIA-E in the placebo-controlled period of AACI had 3 or more episodes of ARIA-E.

Similar findings were observed in the placebo-controlled pool (difference no greater than 1%) and the all-donanemab pool (difference no greater than 2%).

The following table shows the incidence of subjects with multiple episodes of ARIA-E in the placebo-controlled period of AACI. The reader is referred to the [Appendix](#) for a table for the placebo-controlled pool.

Table 39. Incidence of Subjects with Multiple Episodes of ARIA-E in the Placebo-controlled Period of AACI

Number of ARIA-E Episodes	Donanemab (N = 201)	Placebo (N = 17)
1	153 (76.1)	17 (100)
2	35 (17.4)	0 (0.0)
3	7 (3.5)	0 (0.0)
4	6 (3.0)	0 (0.0)

This table was created by Senior Clinical Analyst Dr. Rui Li

ARIA and Intracerebral Hemorrhage > 1 cm by ApoE ε4 Genotype Status

ApoE ε4 homozygotes have been previously shown to have an increased incidence of symptomatic and overall ARIA compared to heterozygotes and noncarriers in subjects taking monoclonal antibodies directed against aggregated forms of beta amyloid.

In the placebo-controlled period of AACI and the placebo-controlled pool, donanemab-treated homozygote ApoE ε4 carriers had an increased incidence of ARIA, ARIA-E, and ARIA-H Microhemorrhage, and ARIA-H superficial siderosis compared to heterozygotes and noncarriers. Homozygous carriers in the all-donanemab pool had similar incidences of ARIA, ARIA-E, ARIA-H, ARIA-H Microhemorrhage, and ARIA-H Superficial siderosis (difference no greater than 6%) compared to the placebo-controlled period of AACI.

Limited numbers of events of intracerebral hemorrhage > 1 cm (n=4, within 57 days of a dose) in the placebo-controlled period of AACI preclude a conclusion being drawn regarding the impact of donanemab in ApoE ε4 carriers on incidence of intracerebral hemorrhage > 1 cm. Additionally, two of the four donanemab-treated subjects with intracerebral hemorrhage > 1 cm had concomitant medication use with an antithrombotic, which further limits a conclusion being drawn of the effect of ApoE ε4 status on incidence of intracerebral hemorrhage. ApoE ε4 alleles have been associated with an increased risk of intracerebral hemorrhage.⁴⁵

The following table shows incidence of ARIA and intracerebral hemorrhage > 1 cm within 57 days of a dose, by ApoE ε4 status in the placebo-controlled period of AACI. The reader is referred to the Appendix for analyses of the incidence of ARIA and intracerebral hemorrhage > 1 cm in the [placebo-controlled pool](#).

Table 40. ARIA and Intracerebral Hemorrhage > 1 cm by ApoE ε4 status in the Placebo-controlled Period of AACI^a

	NonCarrier		Heterozygotes		Homozygotes	
	DON N=255 n (%)	PBO N=250 n (%)	DON N=452 n (%)	PBO N=474 n (%)	DON N=143 n (%)	PBO N=146 n (%)
ARIA-E or ARIA-H	63 (24.7)	29 (11.6)	164 (36.3)	60 (12.7)	79 (55.2)	32 (21.9)
ARIA-E	40 (15.7)	2 (0.8)	102 (22.6)	9 (1.9)	58 (40.6)	5 (3.4)
ARIA-H	48 (18.8)	27 (10.8)	142 (31.4)	54 (11.4)	72 (50.3)	30 (20.5)
ARIA-H Microhemorrhages	39 (15.3)	26 (10.4)	117 (25.9)	48 (10.1)	60 (42.0)	26 (17.8)

⁴⁵ Marini et al. Association of Apolipoprotein E With Intracerebral Hemorrhage Risk by Race/Ethnicity. JAMA Neurol. 2019;76(4):480-491. doi:10.1001/jamaneurol.2018.4519

	NonCarrier		Heterozygotes		Homozygotes	
	DON N=255 n (%)	PBO N=250 n (%)	DON N=452 n (%)	PBO N=474 n (%)	DON N=143 n (%)	PBO N=146 n (%)
ARIA-H Superficial Siderosis	19 (7.5)	2 (0.8)	70 (15.5)	10 (2.1)	36 (25.2)	11 (7.5)
Intracerebral hemorrhage > 1 cm ^b	1 (0.4)	0	3 (0.7)	1 (0.2)	0	0

^aThe incidence of ARIA is based on analyses using the MRI dataset provided by Senior Clinical Analyst Dr. Rui Li. The incidence of intracerebral hemorrhage > 1 cm is based on analyses using the combined adverse event, MRI datasets, and a review of narratives performed by this reviewer.

^bOne placebo-treated subject with intracerebral hemorrhage > 1 cm had unknown ApoE genotype status (15T-MC-AACI- (b) (6)).

ApoE ε4 Genotype Status and Clinical Outcomes of ARIA and Intracerebral Hemorrhage > 1 cm

The incidence of symptomatic ARIA-E, SAEs of ARIA-E and ARIA-H, and discontinuations and treatment interruptions were greater in homozygotes than in heterozygotes or noncarriers of ApoE ε4 as shown in the following table. The number of subjects with intracerebral hemorrhage > 1 cm was low, and a conclusion regarding the effect of ApoE ε4 status on clinical outcomes of intracerebral hemorrhage cannot be drawn. Similar findings were observed in the placebo-controlled pool ([Appendix](#)).

Table 41. Serious ARIA and Intracerebral Hemorrhage > 1 cm, Symptomatic ARIA, Treatment Discontinuations and Treatment Interruptions due to ARIA and Intracerebral Hemorrhage > 1 cm by ApoE ε4 status in the Placebo-controlled Period of AACI

Events	Donanemab N=853		
	Noncarriers N=255 n (%)	Heterozygotes N=452 n (%)	Homozygotes N=143 n (%)
ARIA-E			
Serious	1 (0.4)	8 (1.8)	4 (2.8)
Treatment Discontinuations	3 (1.2)	10 (2.2)	8 (5.6)
Treatment Interruptions	26 (10.2)	74 (16.4)	43 (30.1)
Symptomatic ^a	10 (3.9)	30 (6.6)	12 (8.4)
ARIA-H			
Serious	1 (0.4)	1 (0.2)	2 (1.4)
Treatment Discontinuations	2 (0.8)	4 (0.9)	2 (1.4)
Treatment Interruptions	14 (5.5)	61 (13.5)	41 (28.7)
Intracerebral Hemorrhage > 1 cm ^b			
Serious	0	1 (0.2)	0

Treatment Discontinuations	0	2 (0.4)	0
Treatment Interruptions	0	1 (0.2)	0

This reviewer created this table using the 90-Day Safety IDB ADAE dataset, TEPCLDFL, APERIODC= First treatment period, STUDYID=AACI. For serious: AESER = Y. For treatment status: AEACN = treatment withdrawn or treatment disrupted.

^aThis reviewer created this using the 90-Day Safety IDB ADCE dataset, TEPCLDFL, STUDYID = AACI.

^bSubject IST-MC-AACI- (b) (6), a noncarrier for ApoE ε4, with events of hemorrhagic stroke and hematoma is not included in the table above as neither event was recorded as an adverse event.

ApoE ε4 Genotype Status and Radiographic Severity of ARIA (MRI dataset)

In the placebo-controlled period of AACI, donanemab-treated subjects homozygous for ApoE ε4 had higher incidences of radiographically severe ARIA, ARIA-E, ARIA-H, ARIA-H Microhemorrhage, and ARIA-H Superficial siderosis compared to heterozygous and non-carriers (the following table). Among subjects treated with donanemab, the rate of severe radiographic ARIA-E was highest in ApoE ε4 homozygotes 3% (4/143) compared to heterozygotes 2% (9/452) or noncarriers 0.4% (1/255). Among subjects treated with donanemab, the rate of severe radiographic ARIA-H was highest in ApoE ε4 homozygotes 22% (31/143) compared to heterozygotes 8% (38/452) or noncarriers 4% (9/255). Similar findings were observed in the placebo controlled pool ([Appendix](#)) and in the all-donanemab pool.

Table 42. ARIA Radiographic Severity by ApoE ε4 Status in the Placebo-controlled Period of AACI (MRI dataset).

	NonCarrier		Heterozygotes		Homozygotes	
	DON N=255 n (%)	PBO N=250 n (%)	DON N=452 n (%)	PBO N=474 n (%)	DON N=143 n (%)	PBO N=146 n (%)
Total Subjects with Any ARIA Events						
Mild	31 (12.2)	24 (9.6)	64 (14.2)	52 (11.0)	24 (16.8)	24 (16.4)
Moderate	22 (8.6)	3 (1.2)	60 (13.3)	8 (1.7)	22 (15.4)	7 (4.8)
Severe	10 (3.9)	2 (0.8)	40 (8.8)	0	33 (23.1)	1 (0.7)
ARIA-E						
Mild	13 (5.1)	2 (0.8)	31 (6.9)	8 (1.7)	14 (9.8)	4 (2.7)
Moderate	26 (10.2)	0	62 (13.7)	1 (0.2)	40 (28.0)	1 (0.7)
Severe	1 (0.4)	0	9 (2.0)	0	4 (2.8)	0
ARIA-H						
Mild	34 (13.3)	22 (8.8)	70 (15.5)	47 (9.9)	30 (21.0)	23 (15.8)
Moderate	5 (2.0)	3 (1.2)	34 (7.5)	7 (1.5)	11 (7.7)	6 (4.1)
Severe	9 (3.5)	(0.8)	38 (8.4)	0	31 (21.7)	1 (0.7)
ARIA-H, Microhemorrhages						
Mild	35 (13.7)	22 (8.8)	78 (17.3)	42 (8.9)	29 (20.3)	24 (16.4)

	NonCarrier		Heterozygotes		Homozygotes	
	DON N=255 n (%)	PBO N=250 n (%)	DON N=452 n (%)	PBO N=474 n (%)	DON N=143 n (%)	PBO N=146 n (%)
Moderate	3 (1.2)	3 (1.2)	22 (4.9)	6 (1.3)	9 (6.3)	2 (1.4)
Severe	1 (0.4)	1 (0.4)	17 (3.8)	0	22 (15.4)	0
ARIA-H, Superficial Siderosis						
Mild	7 (2.7)	1 (0.4)	26 (5.8)	9 (1.9)	14 (9.8)	6 (4.1)
Moderate	4 (1.6)	0	20 (4.4)	1 (0.2)	8 (5.6)	4 (2.7)
Severe	8 (3.1)	1 (0.4)	24 (5.3)	0	14 (9.8)	1 (0.7)

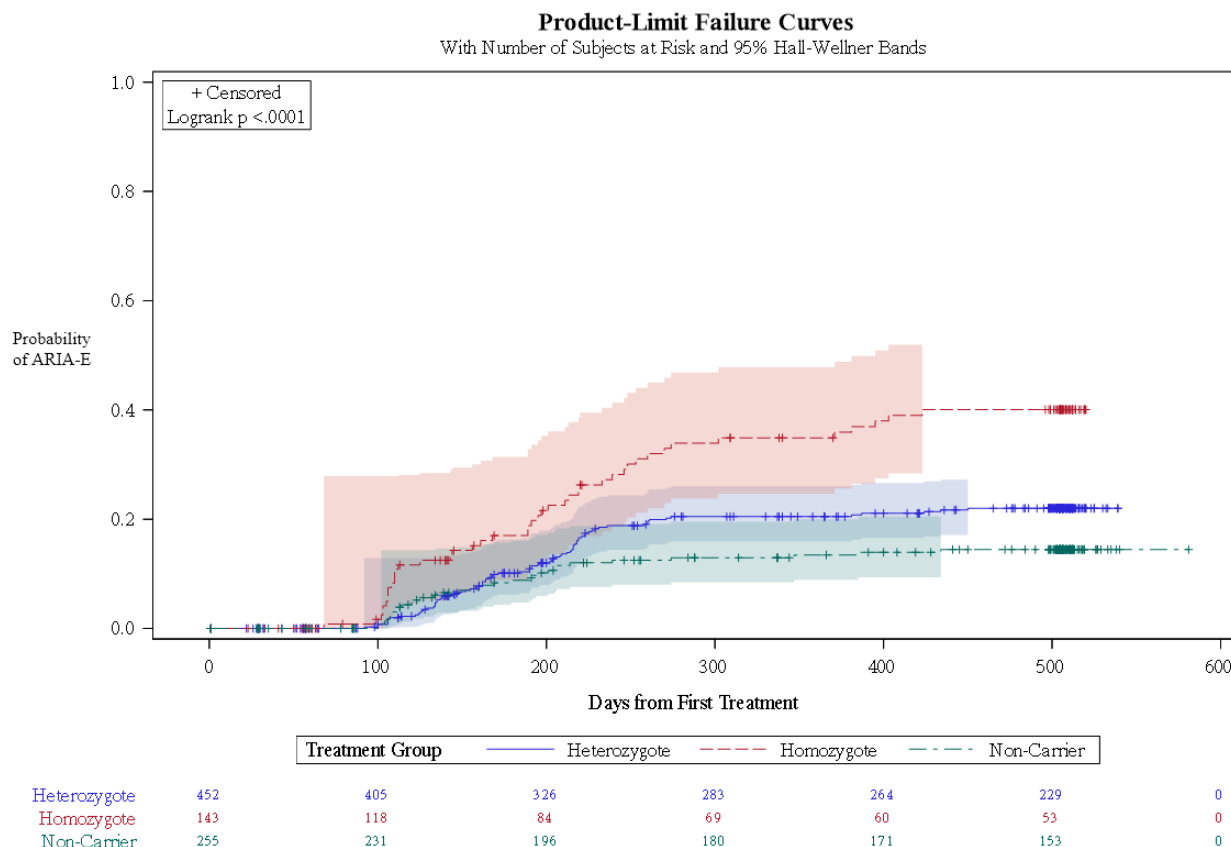
The reviewer created this table using analyses by Senior Clinical Analyst Dr. Rui Li.

ApoE ε4 Genotype Status and Timing of ARIA (MRI dataset)

Homozygous ApoE ε4 carriers had similar incidences of developing ARIA-E within the first three and first six doses compared to all donanemab-treated subjects in the placebo-controlled pool (differences no greater than 2%). The reader is referred to the [Appendix](#) for analyses related to number of doses received to first ARIA-E in ApoE ε4 carriers.

Among donanemab-treated subjects homozygous for ApoE ε4, the majority of first ARIA-E events had occurred by 400 days from first treatment in the placebo-controlled period of AACI (approximately 15 doses). The following plot shows the probability of first ARIA-E event by ApoE ε4 status among donanemab-treated subjects in the placebo-controlled period of AACI.

Figure 5. Probability of First ARIA-E Event for the Placebo-controlled Period of AACI (MRI dataset)



The above figure was created by Senior Clinical Analyst Dr. Rui Li.

Similar findings were observed for the placebo-controlled pool. The reader is referred to the [Appendix](#) for a plot showing time to first ARIA-E event by ApoE ε4 status among donanemab-treated subjects in the placebo-controlled pool.

Other Risk Factors for ARIA

In analyses of the placebo-controlled pool submitted by the Applicant, donanemab-treated subjects with microhemorrhage or superficial siderosis on baseline MRI had a higher incidence of ARIA compared to subjects without those findings on baseline MRI (53.1% [78/147] versus 33.3% [279/837], respectively).⁴⁶

⁴⁶ Noted on page 1073 of the Applicant's response dated October 10, 2023, to an information request dated October 2, 2023.

In analyses of the placebo-controlled pool submitted by the Applicant, donanemab-treated subjects with white matter disease present on baseline MRI had higher incidence of ARIA in compared to subjects without those findings (37.4% [333/890] versus 25.5% [24/94], respectively).⁴⁷

Using the data from the all-donanemab pool, the applicant identified the presence of 2-4 microhemorrhages at baseline and presence of 1 area of superficial siderosis at baseline as risk factors for ARIA-E and for ARIA-H, in addition to the number of ApoE ε4 alleles.⁴⁸ Of note, there are limitations of these analyses in that the study excluded patients with severe white matter lesions, more than 4 microhemorrhages, and more than 1 area of superficial siderosis. Nevertheless, the risk factors were able to be identified, even with more severe pathology excluded.

Table 43. Baseline Microhemorrhage and Superficial Siderosis as Risk Factors for ARIA in the All-Donanemab Pool

Event	2-4 microhemorrhages at baseline	1 area of superficial siderosis at baseline
	Odds ratio (95% CI), p value	Odds ratio (95% CI), p value
ARIA-E	2.32 (1.45-3.69), p<0.001	2.35 (1.28-4.28) p=0.005
ARIA-H	4.28 (2.69-6.93), p < 0.001	3.46 (1.89-6.47) p < 0.001

Above data taken from Applicant's analyses noted in Figure 5.2 and 5.4 of the RSUR submitted June 12, 2023.

Antithrombotic Use and Incidence of ARIA-H and Intracerebral Hemorrhage > 1 cm (MRI dataset)

In studies AACH, AACG, and AACI, antithrombotic use was allowed. In AACN, patients were excluded if they were on anticoagulants or antiplatelets, except for aspirin less than or equal to 325 mg daily. For the following analyses, subjects were considered to have used antithrombotics if they reported use within 30 days prior to an event of ARIA-H or intracerebral hemorrhage > 1 cm.

The following table shows the incidence of ARIA-H and of intracerebral hemorrhage > 1 cm by antithrombotic use status in the placebo-controlled period of AACI. The incidence of ARIA-H was slightly greater in donanemab-treated subjects on antithrombotics compared to those not on antithrombotics (30.4% versus 29.4%, respectively). The incidence of intracerebral hemorrhage > 1 cm in donanemab-treated subjects on antithrombotics was slightly greater than in those not on antithrombotics (0.6% versus 0.4%, respectively). Similar findings of

⁴⁷ Noted on page 1073 of the Applicant's response dated October 10, 2023, to an information request dated October 2, 2023.

⁴⁸ Resubmission update of safety information, section 5.5.9.1.4., pp 142-147, submitted June 12, 2023.

incidence were observed in the placebo-controlled pool ([Appendix](#)). Of note, the four subjects with intracerebral hemorrhage > 1 cm had risk factors that predispose to intracerebral hemorrhage, limiting the interpretation of these findings.⁴⁹

Table 44. Incidence of Subjects with ARIA-H or Intracerebral Hemorrhage > 1 cm by Antithrombotic Use in the Placebo-controlled Period of AACI

Event ^a	Donanemab		Placebo	
	AT use N=349 n (%)	No AT Use N=504 n (%)	AT use N=361 n (%)	No AT Use N=513 n (%)
ARIA-H	106 (30.4)	148 (29.4)	47 (13.3)	63 (12.3)
Intracerebral Hemorrhage > 1 cm ^b	2 (0.6)	2 (0.4)	0	2 (0.4)

AT: Antithrombotic

^aSubjects are considered to have ARIA-H or intracerebral hemorrhage occurring in the setting of antithrombotic use if they: 1) had an event while on an antithrombotic or 2) had used an antithrombotic within 30 days prior to an event.

^bThe donanemab arm includes I5T-MC-AACI- (b) (6) I5T-MC-AACI- (b) (6) I5T-MC-AACI- (b) (6) and I5T-MC-AACI- (b) (6)

No increased incidence of ARIA-H was observed in subjects with concomitant use of an anticoagulant or aspirin greater than 81 mg daily/antiplatelet/aspirin plus antiplatelet compared to subjects with use of aspirin less than or equal to 81 mg daily. The majority of exposures to antithrombotics in the donanemab arm were to aspirin, antiplatelet, or aspirin in combination with an antiplatelet (80%, 331/414). The number of events and limited exposure to non-aspirin antithrombotic medications limit definitive conclusions about the risk of ARIA or intracerebral hemorrhage in subjects taking antithrombotic medications. Similar findings of incidence were observed in the placebo-controlled pool ([Appendix](#)).

Table 45. Incidence of Subjects with ARIA-H or Intracerebral Hemorrhage > 1 cm by Antithrombotic Class Use in the Placebo-controlled Period of AACI^a

Event ^b	Donanemab	Placebo

⁴⁹Risk factors for cerebral hemorrhage in donanemab-treated participants: I5T-MC-AACI- (b) (6): ApoE ε4 allele. Additionally, the participant may have had cerebral amyloid angiopathy (CAA), based on focal white matter disease on screening MRI, and development of superficial siderosis and 2 microhemorrhages postbaseline. I5T-MC-AACI- (b) (6): ApoE ε4 allele. Additionally, the participant may have had CAA, based on focal white matter disease at screening, and development of superficial siderosis and 3 microhemorrhages postbaseline. I5T-MC-AACI- (b) (6): ApoE ε4 allele, focal white matter disease; blood pressure greater than 130/80. Additionally, the participant may have had CAA, based on focal white matter and superficial siderosis on screening MRI. I5T-MC-AACI- (b) (6) Hypertension. Additionally, the participant may have had CAA, based on beginning confluence of white matter lesions and superficial siderosis on screening.

	ASA ≤ 81 mg N=261 n (%)	ASA > 81 or APT or ASA and APT N=70 n (%)	AC N=83 n (%)	ASA ≤ 81 mg N=260 n (%)	ASA > 81 or APT or ASA and APT N=62 n (%)	AC N=86 n (%)
ARIA-H	83 (31.8)	15 (21.4)	20 (24.1)	35 (13.5)	10 (16.1)	11 (12.7)
Intracerebral Hemorrhage > 1 cm ^c	0	2 (2.9)	0	0	0	0

AC: Anticoagulant, APT: Antiplatelet therapy, ASA: Aspirin.

^aA subject can contribute to multiple antithrombotic classes.

^bSubjects are considered to have ARIA-H or intracerebral hemorrhage occurring in the setting of antithrombotic use if they: 1) had an event while on an antithrombotic or 2) had used an antithrombotic within 30 days prior to an event.

^cThe donanemab arm includes I5T-MC-AACI- (b) (6) (prasugrel 10 mg daily) and I5T-MC-AACI- (b) (6) (several acetylsalicylic acid tablets, amount not specified).

Thrombolytic Use and Intracerebral Hemorrhage

One donanemab-treated subject developed intracerebral hemorrhage with fatal outcome in the setting of thrombolytic use (tenecteplase) for symptoms mimicking stroke in the setting of ARIA-E (intracerebral hemorrhage, I5T-MC-AACI- (b) (6)). 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. The case is discussed further in the Deaths section of this review.

Concomitant administration of tPA was reported for 3 additional subjects, none of whom had intracerebral hemorrhage (donanemab: I5T-MC-AACI- (b) (6) and placebo: I5T-MC-AACI- (b) (6) and I5T-MC-AACI- (b) (6)). The donanemab-treated subject had fatal outcome from complications of Covid-19, and also experienced cerebral infarction in the setting of atrial fibrillation. The case is discussed further in the Deaths section of this review.

8.5.3. Seizure

The incidence of seizures was greater in donanemab-treated subjects compared to placebo in the setting of ARIA as well as independent of ARIA in the placebo-controlled period of AACI and the placebo-controlled pool. No events of status epilepticus were observed.

Method

For the following analyses, this reviewer analyzed seizures recorded in the adverse event dataset and the clinical event analysis dataset, which recorded any symptoms associated with ARIA. For events of intracerebral hemorrhage, this reviewer analyzed events recorded in both

the adverse event dataset and the MRI dataset. For events of ARIA, this reviewer analyzed ARIA events recorded in the adverse event dataset, which this reviewer considered to be the most comprehensive source for recording symptoms associated with ARIA.

A higher incidence of seizure was observed in donanemab-treated subjects compared to placebo in the placebo-controlled period of AACI (1.2% versus 0.3%, respectively). Among donanemab-treated subjects with seizure, seizure as a symptom of ARIA-E accounted for 50% of the cases (5/10). An imbalance in serious cases of seizure was observed in donanemab-treated subjects compared to placebo (0.4% versus 0.1%, respectively). No cases of seizure were reported in the setting of intracerebral hemorrhage in the placebo-controlled period of AACI. A higher incidence of seizure occurring independently of either ARIA or intracerebral hemorrhage was observed among donanemab-treated subjects compared to placebo in the placebo-controlled period of AACI (0.6% versus 0.3%, respectively). Similar findings were observed for the placebo-controlled pool. A similar incidence of seizure was observed in the all-donanemab pool compared to the placebo-controlled period of AACI (difference no greater than 0.5%). No events of status epilepticus were reported.

The following table shows the incidence of seizure, seizure with ARIA-E, and seizure with intracerebral hemorrhage in the placebo-controlled period of AACI. The reader is referred to the [Appendix](#) for tables for the placebo-controlled pool and the all-donanemab pool.

Table 46. Incidence of Seizure, Seizure with ARIA-E, and Seizure with Intracerebral Hemorrhage in the Placebo-Controlled Period of AACI

AEs	Donanemab N=853 n (%)	Placebo N=874 n (%)
Seizure	10 (1.2)	3 (0.3)
Serious seizure ^a	3 (0.4)	1 (0.1)
Seizure with ARIA-E ^a	5 (0.6)	0
Seizure with intracerebral hemorrhage	0	0
Serious seizure with intracerebral hemorrhage	0	0
Seizure without either ARIA or intracerebral hemorrhage	5 (0.6)	3 (0.3)
Serious seizure without either ARIA or intracerebral hemorrhage ^a	2 (0.2)	1 (0.1)

This reviewer created this table using the 90-Day Safety Update ADAE and ADCE datasets.

^aSeizures recorded as a symptom of ARIA in the ADCE dataset were not assessed for seriousness.

Narratives

This reviewer identified nine SAEs related to the topic seizure, occurring in 8 subjects in the all-donanemab pool using the within treatment period plus 57 days analysis method.

In one case, this reviewer did not establish a role for donanemab in the event of seizure as the event occurred more than 200 days after the last dose of study drug (I5T-MC-AACI- (b) (6)).

In a review of narratives, this reviewer noted one additional subject with seizure that occurred in the setting of ARIA-E with fatal outcome (I5T-MC-AACI- (b) (6)).⁵⁰ In this case, the cause of death was reported as secondary to symptomatic ARIA-E, aggravated by seizures.

In one case, seizure occurred in the setting of ARIA-E and 5 new microhemorrhages in a subject with a total of 23 microhemorrhages and with superficial siderosis and resulted in discontinuation of donanemab (I5T-MC-AACI- (b) (6)).

In one case, the seizure occurred in a subject who had developed diabetic ketoacidosis (I5T-MC-AACI- (b) (6)).

In two cases, this reviewer did not rule out a role for donanemab given the imbalance in seizure noted in the placebo-controlled pool. In these two cases, the subjects continued to receive donanemab without experiencing further seizures (I5T-MC-AACI- (b) (6) and I5T-MC-AACI- (b) (6)).

In the remaining cases of seizure, although a role for donanemab could not be ruled out given the imbalance noted in the placebo-controlled pool, this reviewer identified other potential contributory factors, including recent event of hemorrhagic stroke (I5T-MC-AACI- (b) (6)), metabolic encephalopathy and Covid-19 infection (I5T-MC-AACI- (b) (6)), and falls/subarachnoid bleed/subdural hygromas/moderate ARIA-H (I5T-MC-AACI- (b) (6)). The reader is referred to the [Appendix](#) for a narrative for this case.

8.5.4. Hypersensitivity and Infusion Related Reactions

Infusion related reactions were among the most frequently reported TEAEs in the placebo-controlled period of AACI, occurring in 8.7% of donanemab-treated subjects compared to 0.5% on placebo. Symptoms associated with infusion-related reactions included: chills, erythema, nausea/vomiting, dyspnea, sweating, elevated blood pressure, headache, chest pain, and low blood pressure. Hypersensitivity reactions other than infusion related reactions occurred in 2.9% of donanemab-treated subjects compared to 0.7% on placebo and included anaphylaxis and angioedema. Most infusion-related reactions and other hypersensitivity reactions were

⁵⁰ Event not recorded in the adverse event or symptomatic ARIA-E dataset.

mild or moderate in severity in the placebo-controlled period of AACI, the placebo-controlled pool, and the all-donanemab pool. Serious cases of infusion related reactions and other hypersensitivity events included cases with increases and decreases in blood pressure and increases in heart rate at the time of infusion or within minutes following the end of the infusion. In one case, increases in blood pressure in the setting of infusion reactions was associated with myocardial infarction.

Method

The Applicant's method for analysis of adverse events related to the topic of hypersensitivity and infusion related reactions included evaluations of TEAEs belonging to the SMQs of Anaphylactic Reaction (Narrow), Hypersensitivity (Narrow), and Angioedema (Narrow).

Reviewer comment: Overall, this reviewer found the Applicant's approach to be acceptable.

Infusion Related Reactions

The incidence of infusion related reaction TEAEs, SAEs of infusion related reactions, and reactions leading to study withdrawal or treatment discontinuation were greater in donanemab-treated subjects compared to placebo in the placebo-controlled period of AACI as shown in the table below. Similar findings were observed in donanemab-treated subjects in the placebo-controlled pool and in the all-donanemab pool.

The following table shows the incidence of TEAEs of infusion related reactions in the placebo-controlled period of AACI. The reader is referred to the [Appendix](#) for a table for the placebo-controlled pool.

Table 47. TEAEs of Infusion Related Reactions in the Placebo-Controlled Period of AACI

Preferred Term	Donanemab N=853 n (%)	Placebo N=874 n (%)
TEAEs	74 (8.7)	4 (0.5)
Serious	1 (0.1)	0
Reported to Lead to Study Withdrawal	19 (2.2)	0
Reported to Lead to Treatment Discontinuation	31 (3.6)	0

This table was created by this reviewer using the 90Day Safety Update ADAE dataset, TEPCDLFL =Y, APERIODC = First Treatment period, AEDECOD= infusion related reaction, AESER = Y or DISAEFL = Y or AEACN = Drug Withdrawn, STUDYID = AACI.

Among donanemab-treated subjects who reported infusion related reactions in the placebo-controlled period of AACI, the maximum severity of infusion related reactions was mild in 56.8% of cases and moderate in 39.2% of cases ([Appendix](#)).

The majority (70/74) of TEAEs of infusion related reaction occurred within 24 hours of an infusion of donanemab in the placebo-controlled period of AACI. Similar findings were observed in the placebo-controlled pool and all-donanemab pool.

Most symptoms of infusion related reactions were reported during drug administration or within 30 minutes of the end of a study drug administration in the placebo-period of AACI, the placebo-controlled pool and the all-donanemab pool ([Appendix](#)).

The majority of donanemab-treated subjects who experienced TEAEs of infusion related reaction had their first event by the fourth dose in the placebo-controlled period of AACI and the placebo-controlled pool (70.3% for both). In the all-donanemab pool, the majority of donanemab-treated subjects had their first event by the third dose (58.1%) ([Appendix](#)).⁵¹

Chills, erythema, nausea/vomiting were the most frequent symptoms reported with infusion related reactions in the placebo-controlled period of AACI. Other signs and symptoms included difficulty breathing/dyspnea, sweating, elevated blood pressure, headache, chest pain, and low blood pressure. The reader is referred the [Appendix](#) for a table of the most frequent symptoms reported with infusion related reactions in the placebo-controlled period of AACI.

Refer to the [Appendix](#) for narratives of SAEs of infusion related reactions. This reviewer noted the following three cases in the all-donanemab pool where infusion reactions were likely contributory to the development of SAEs.

Table 48. Additional SAEs associated with Infusion Related Reactions in the All-Donanemab Pool

Subject	Preferred Term	Description	Timing	Risk Factors
I5T-MC-AACI- (b) (6)	Acute myocardial infarction (verbatim term non-ST elevation MI with atypical chest pain)	Increased blood pressure to 217/117 mm Hg (compared to 150/80 mmHg pre-dose)	During infusion of 3 rd dose.	PMH of hypertension, hyperlipidemia; 30-40% occlusion of left anterior descending artery; with mitral

⁵¹ Data submitted by the Applicant in a response dated January 9, 2024, to an information request dated January 4, 2024

Subject	Preferred Term	Description	Timing	Risk Factors
				regurgitation on day of event.
15T-MC-AACI- (b) (6)	Angina pectoris	Increased blood pressure to 168/108 mmHg (compared to 139/78 mm Hg pre-dose); no acute changes on ECG.	During infusion of 5 th dose; similar event during infusion of 6 th dose	PMH of coronary artery disease; hypertension.
15T-AACI- (b) (6)	Respiratory distress	Difficulty breathing; Increased blood pressure to 142/90 mm Hg, heart rate 118 bpm; oxygen saturation 82% (predose blood pressure of 122/76; heart rate 79 bpm).	During infusion of 3rd dose. Similar difficulty breathing during 2 nd infusion.	None identified

Interventions for Infusion Related Reactions

The following information was provided by the Applicant in the 90-Day Safety Update Resubmission Safety Update Report dated September 9, 2023 (Section 4.5.1.2.4 Infusion-Related Reactions and Interventions, page 84).

The Applicant noted that interventions for infusion related reactions included administration of medications prior to infusion and slowing of the infusion on or after the infusion related reaction.

Pretreatment medications for infusion related reactions included antihistamines, acetaminophen, and corticosteroids.

The Applicant compared the incidence of infusion related reactions among subjects who received medications pretreatment upon rechallenge to subjects who did not receive pretreatment medication upon rechallenge in the all-donanemab pool.

In the all-donanemab pool, of the 266 subjects with an infusion related reaction, 68% (181/266) had a subsequent infusion. Similar incidences of infusion related reactions were observed in subjects who received pretreatment medication upon rechallenge (38.1%, 16/42) compared to those who did not receive pretreatment medication on rechallenge (41.0%, 57/139; [Appendix](#)). However, the number of subjects receiving pretreatment medication was too few to draw conclusions.

In the all-donanemab pool, similar incidences of infusion related reactions were observed in subjects who had infusions slowed upon rechallenge (40.3% [31/77]) compared to those who did not have infusions slowed on rechallenge (40.4% [42/104]; [Appendix](#)).

Other Hypersensitivity Events

In order to evaluate other hypersensitivity events other than infusion related reaction, this reviewer searched the adverse event dataset used the SMQ Hypersensitivity (narrow). This reviewer's evaluation also included grouping of similar preferred terms within the Hypersensitivity SMQ.

There is no imbalance in dermatitis/eczema or allergic rhinitis and little imbalance in rash between donanemab and placebo in the placebo-controlled period and the placebo-controlled pool ([Appendix](#)).

Excluding those terms (where no or little imbalance was observed) or preferred terms not reported in donanemab-treated subjects,⁵² other events within the SMQ of Hypersensitivity were reported in 2.9% of donanemab-treated subjects versus 0.7% on placebo. Events occurring in donanemab-treated subjects included angioedema and anaphylaxis.

The incidence of grouped terms related to angioedema, including eye edema, eyelid edema, face edema, lip swelling, and urticaria, was greater among donanemab-treated subjects (1.2%, 10/853) compared to placebo (0.5%, 4/874) in the placebo-controlled period of AACI and the placebo-controlled pool ([Appendix](#)). Similar findings of the incidence of angioedema among donanemab-treated subjects in the placebo-controlled pool and the all-donanemab pool were observed (difference no greater than 0.3%).⁵³ Anaphylactic reactions occurred in 0.4% (3/853) in donanemab-treated subjects and none in placebo in the placebo-controlled period of AACI .

⁵²In the placebo-controlled period of AACI, two events were reported in the placebo arm: Circulatory collapse (where dehydration was suspected [I5T-MC-AACI- (b) (6)]) and urticarial vasculitis (I5T-MC-AACI- (b) (6)).

⁵³The incidences do not include two events of angioedema occurring in donanemab-treated participants that were not recorded as AEs in the adverse event dataset: mouth swelling (recorded in the ADAEFA dataset in the placebo-controlled period of AACI [I5T-MC-AACI- (b) (6)]) and lip swelling (recorded in the narrative in the long-term extension period of AACI [I5T-MC-AACI- (b) (6)]).

Table 49. TEAEs of Hypersensitivity (includes Anaphylaxis and Grouped Terms of Hypersensitivity and Angioedema) in the Placebo-Controlled Period of AACI

Preferred Term	Donanemab N=853 n (%)	Placebo N=874 n (%)
Other TEAEs of Hypersensitivity SMQ	25 (2.9)	6 (0.7)
Grouped Terms Related to Hypersensitivity ^a	12 (1.4)	2 (0.2)
Grouped Terms Related to Angioedema	10 (1.2)	4 (0.5)
Eyelid edema	2 (0.2)	0
Face edema	2 (0.2)	0
Angioedema	2 (0.2)	1 (0.1)
Eye edema	1 (0.1)	0
Lip swelling	1 (0.1)	0
Swelling face	0	1 (0.1)
Urticaria	3 (0.4)	1 (0.1)
Urticaria papular	0	1 (0.1)
Anaphylactic reaction	3 (0.4)	0

The reviewer created this table using the 90Day Safety Update ADAE, TEPCLDL, APERIODC = First Treatment period, SMQ13SC = Narrow, STUDYID = AACI.

^aInfusion related hypersensitivity reaction and infusion site hypersensitivity

The following section contains analyses related to TEAEs belonging to the Hypersensitivity SMQ (narrow) with the preferred term of Infusion related reaction excluded, as infusion related reactions are discussed separately above.

Serious TEAEs, excluding infusion related reaction, belonging to the Hypersensitivity SMQ were reported in 0.2% of donanemab-treated subjects compared to 0.1% on placebo. Among donanemab-treated subjects, TEAEs led to study withdrawal in 0.4% (3/853) and to treatment discontinuation in 1.1% (9/853) compared to none on placebo. Similar findings were observed in donanemab-treated subjects in the placebo-controlled pool and the all-donanemab pool ([Appendix](#)).

Most subjects had maximum severity of mild or moderate for TEAEs, excluding infusion related reaction, belonging to the Hypersensitivity SMQ in the placebo-controlled period of AACI, the placebo-controlled pool and the all-donanemab pool ([Appendix](#)).

The majority of TEAEs, excluding infusion related reaction, belonging to the Hypersensitivity SMQ occurred greater than 24 hours from an infusion in the placebo-controlled period of AACI. Similar findings were observed in the placebo-controlled pool and all-donanemab pool.

The following table shows the incidence of TEAEs, excluding infusion related reaction, belonging to the Hypersensitivity SMQ occurring within 24 hours of an infusion in the placebo-controlled period of AACI. The reader is referred to the [Appendix](#) for a table for the placebo-controlled pool.

Table 50. Incidence of TEAEs of Hypersensitivity Other than Infusion Related Reactions Occurring Within 24 Hours of an Infusion in the Placebo-controlled Period of AACI.

TEAEs	Donanemab N=853 n (%)	Placebo N=874 n (%)
TEAEs	62 (7.3)	44 (5.0)
TEAEs within 24 Hours	19 (2.2)	6 (0.7)

This table was created by this reviewer using the 90Day Safety Update ADAE dataset, TEPCDLFL =Y, APERIODC = First Treatment period, SMQ13SC = Narrow, AEDECOD = inverse of infusion related reaction, AEDOSEFL =Y, STUDYID = AACI.

A majority of donanemab-treated subjects reported their first event of hypersensitivity other than infusion related reaction before the sixth dose in the placebo-controlled period of AACI. Similar findings were observed for the placebo-controlled pool (62.1% before the 6th dose) and the all-donanemab pool (62.5% before the 6th dose).⁵⁴ The reader is referred to the [Appendix](#) for tables for the placebo-controlled period of AACI and the placebo-controlled pool.

Cases of Anaphylaxis

This reviewer identified 15 cases related to the topic of anaphylaxis in the all-donanemab pool.

Based on clinical criteria developed by Sampson et al. 2006 to identify cases of anaphylaxis,⁵⁵ and a review of narratives or verbatim symptoms reported with the adverse events, this reviewer assessed 10 of the 15 cases as likely cases of anaphylaxis: anaphylactic reaction ([I5T-MC-AACI-](#)^{(b) (6)} [I5T-MC-AACI-](#)^{(b) (6)} [I5T-MC-AACI-](#)^{(b) (6)} [I5T-MC-AACI-](#)^{(b) (6)}), infusion related reaction ([I5T-MC-AACI-](#)^{(b) (6)} [I5T-MC-AACI-](#)^{(b) (6)} and [I5T-MC-AACI-](#)^{(b) (6)}), and anaphylactic shock ([I5T-MC-AACI-](#)^{(b) (6)}) and the remaining 4 cases as possible cases of anaphylaxis: anaphylactic reaction ([I5T-MC-AACI-](#)^{(b) (6)} and [I5T-MC-AACI-](#)^{(b) (6)}), infusion related hypersensitivity reaction ([I5T-MC-AACI-](#)^{(b) (6)}), and syncope ([I5T-MC-AACI-](#)^{(b) (6)}).

⁵⁴ Data submitted by the Applicant in a response dated January 9, 2024, to an information request dated January 4, 2024

⁵⁵ Sampson H, Munoz-Furlong A, Campbell R, et al. Second symposium on the definition and management of anaphylaxis: summary report-Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. J Allergy Clin Immunol 2006; 117:391-397.

Narratives for additional serious cases belonging to the SMQs of Hypersensitivity (Narrow) are in the [Appendix](#).

8.5.5. Intestinal Obstruction or Intestinal Perforation

An imbalance in TEAEs, all SAEs, of intestinal obstruction (3 cases in the donanemab arm [0.4%] versus no case on placebo)⁵⁶ and intestinal perforation (2 cases in the donanemab arm [0.2%] versus 1 case on placebo [0.1%]) was observed in the placebo-controlled period of AACI. A review of narratives of cases of intestinal obstruction and intestinal perforation showed that most cases had a history of prior surgery as a potential risk factor and many cases also had concomitant use of drugs associated with constipation or intestinal obstruction.

Similar findings were observed in the placebo-controlled pool. All of the TEAEs were serious.

The following table shows TEAEs related to intestinal obstruction or intestinal perforation in the placebo-controlled period of Study AACI.⁵⁷ The reader is referred to the [Appendix](#) for TEAEs of intestinal obstruction or intestinal perforation in the placebo-controlled pool.

Table 51. TEAEs Related to the Intestinal Obstruction or Intestinal Perforation in the Placebo-controlled Period of Study AACI

Preferred Terms and Groups of Preferred Terms	Donanemab N=853 n (%)	Placebo N=874 n (%)
Grouped Terms of Intestinal Obstruction ^a	3 (0.4)	0
Small intestinal obstruction	2 (0.2)	0
Intestinal obstruction	1 (0.1)	0
Grouped Terms of Intestinal Perforation	2 (0.2)	1 (0.1)
Intestinal perforation	1 (0.1)	0
Large intestine perforation	1 (0.1)	0
Small intestinal perforation	0	1 (0.1)

This reviewer created this table using the 90-Day Safety IDB ADAE dataset, StudyID = AACI, TEPCLDFL.

^aThis excludes IST-MC-AACI- (b) (6) who reported small intestinal obstruction more than 6 months from the last dose of donanemab.

⁵⁶ Excluding IST-MC-AACI- (b) (6) who reported small intestinal obstruction more than 6 months from the last dose of donanemab.

⁵⁷ Excluding IST-MC-AACI- (b) (6) who reported small intestinal obstruction more than 6 months from the last dose of donanemab.

In the all-donanemab pool after excluding I5T-MC-AACI- (b) (6) 5 (0.2%) unique subjects reported a TEAE of intestinal obstruction and 5 (0.2%) unique subjects reported a TEAE of intestinal perforation as of the 90-Day Safety Update. Nine of the 10 AEs were serious.

A similar incidence of SAEs related to colitis, hernia, pancreatitis, gastroenteritis, gastric obstruction, lower gastrointestinal hemorrhage, diarrhea, and gastritis/duodenitis were observed in donanemab and placebo arms in the placebo-controlled pool (difference no greater than 0.2%). The reader is referred to the [Appendix](#) for a table related to SAEs related to the Gastrointestinal tract in the placebo-controlled pool.

Incidence of TEAEs belonging to the GI SOC was similar in the donanemab and placebo arms in the placebo-controlled pool (20.9% versus 19.2%, respectively) and the placebo-controlled period of AACI (20.4% versus 19.1%, respectively). Incidence of TEAEs with preferred term of constipation was similar in donanemab and placebo arms in the placebo-controlled pool (1.8% versus 2.3%, respectively) and the placebo-controlled period of AACI (1.9% versus 2.3%, respectively). The reader is referred to the [Appendix](#) for 1) a table of TEAEs by preferred term and groups of preferred terms with incidence of at least 0.3% higher in the donanemab arm compared to placebo in the placebo-controlled pool, 2) a table of select TEAEs and grouped TEAEs belonging to the GI SOC with incidence of less than 0.3% higher in the donanemab arm compared to placebo in the placebo-controlled pool, and 3) a table of the incidence of all TEAEs by preferred term belonging to the GI SOC in the placebo-controlled pool.

Narratives

The following section contains narratives of cases of TEAEs and SAEs of intestinal obstruction and intestinal perforation, serious cases of hernia, and TEAEs and SAEs of colitis. The reader is referred to the Appendix for a review of narratives of other SAEs of the gastrointestinal tract, including [Gastroenteritis](#) and [Gastritis/Duodenitis](#).

TEAEs and SAEs of Intestinal Obstruction and Intestinal Perforation

Using on treatment plus 57 days analysis method, this reviewer identified 11 TEAEs of intestinal obstruction or perforation occurring in 11 subjects. Ten of the 11 AEs were also serious adverse events. In 9 of the 11 subjects in the all-donanemab pool with AEs of intestinal obstruction or intestinal perforation, the outcome of the AE was noted as recovered/resolved and in the remaining two subjects, the AE was noted as recovering/resolving. Seven of the 11 subjects received additional doses of donanemab after the event. In 7 of the 11 cases, the onset of intestinal obstruction and perforation was reported within the first nine doses of donanemab.

Two cases appeared unrelated to donanemab because of timing or concurrent events. One case occurred more than six months after the most recent dose (small intestinal obstruction, I5T-

MC-AACI- (b) (6) in a subject with a past medical history of constipation and small bowel obstruction)⁵⁸ and a second case appeared unrelated as the subject experienced the concurrent event of adenocarcinoma of the colon after the fifth dose of donanemab (large intestine perforation, IST-MC-AACI- (b) (6)).

In one case, a role for donanemab in the event of large intestinal perforation (non-serious, TEAE onset: Study Day 93) could not be established given initiation and increase in dose of amlodipine within 2 months of the TEAE of large intestinal perforation occurring in the setting of sigmoid diverticulitis in a subject with diverticulosis (large intestine perforation, IST-MC-AACI- (b) (6)). Labeling for amlodipine includes a postmarketing side effect of constipation, which may have been contributory to the event of intestinal perforation.⁵⁹

In the remaining eight cases, this reviewer did not rule out a role for donanemab as serious cases of intestinal obstruction and perforation were reported more frequently in donanemab-treated subjects compared to placebo in the placebo-controlled pool. Six of the eight cases required surgery for treatment. Six of the eight subjects had a history of abdominal or pelvic surgery as possible risk factors for the development of intestinal obstruction and perforation. Many cases also had concomitant medication use associated with constipation or intestinal obstruction. Although the cases are confounded, there is an imbalance between donanemab and placebo in ACCI, and the incidence of intestinal obstruction in subjects treated with donanemab, while within a global range reported for individuals 65 to less than 85 years of age of approximately 0.3% to 0.75%⁶⁰, exceeds the incidence of 0.23% and 0.28% reported in subjects with Alzheimer's disease exposed to placebo in other clinical trial settings.⁶¹ The following table summarizes SAEs related to intestinal obstruction and perforation in the eight cases.

Table 52. Summaries of Remaining 8 SAEs Related to Intestinal Obstruction and Perforation in the All-Donanemab Pool

USUBJID Pool	SAE	Comments

⁵⁸ Noted in the Applicant's response dated November 21, 2023, to an information request dated November 20, 2023.

⁵⁹ Norvasc. Labeling-Prescribing Information. Drugs@fda.gov. Action date October 30, 2017. Accessed December 15, 2023.

⁶⁰ Noted in the applicant's response dated January 9, 2024, citing Long D, Mao C, Liu Y, et al. Global, regional, and national burden of intestinal obstruction from 1990 to 2019: an analysis from the Global Burden of Disease Study 2019, *Int J Colorectal Dis.* 2023; 38:245. <https://doi.org/10.1007/s00384-023-04552-6>.

⁶¹ Noted in the applicant's response dated January 9, 2024, citing clinical trials NCT01900665 (solanezumab) and NCT 00676143 (bapineuzumab).

USUBJID Pool	SAE	Comments
I5T-MC-AACI- (b) (6) PC	Small intestinal obstruction	75 yo F who experienced a small intestinal obstruction caused by an incarcerated ventral hernia. She underwent surgical repair. Concomitant medications: loteprednol, verapamil, acyclovir, losartan, donepezil, memantine, brimonidine; timolol, mirtazapine, and pilocarpine. Risk factor: history of cholecystectomy, abdominal mass, repair of abdominal wall, diverticulosis. Constipation is one of the most common adverse reactions of mirtazapine and postmarketing intestinal obstruction has been reported. The AE was reported 21 days after the 5th donanemab dose (received 15 donanemab doses total)
I5T-MC-AACI- (b) (6) PC	Small intestinal obstruction	83 yo F who developed abdominal pain. The CT scan showed distal small bowel closed loop obstruction. She underwent exploratory laparotomy with lysis of adhesions. Concomitant medications: calcium, multivitamins, vitamin B12, vitamin D3, mirtazapine, buspirone, and Dynamic brain vitamins NFI Risk factor: History of cholecystectomy, bladder surgery, and hysterectomy, adhesions noted on exploratory laparotomy.⁶² Constipation is one of the most common adverse reactions of mirtazapine and postmarketing intestinal obstruction has been reported. The AE was reported 29 days after the 15th donanemab dose (received 16 donanemab doses total)
I5T-MC-AACI- (b) (6) PC	Intestinal obstruction	81 yo M who presented with abdominal pain. A CT of abdomen showed dilated stool-filled rectum measuring up to 8.2 cm in maximal diameter. The subject was treated with polyethylene glycol and recovered from the event 3 days later. Risk factor: appendectomy⁶³

⁶² Noted in the Applicant's response dated November 21, 2023, to an information request dated November 20, 2023.

⁶³ Noted in the Applicant's response dated November 21, 2023, to an information request dated November 20, 2023.

USUBJID Pool	SAE	Comments
		Concomitant medications: ubidecarenone, atorvastatin, multivitamins, ascophyllum nodosum; ascorbic acid; betacarotene; borago officinalis; capsicum annuum; petroselinum crispum; pyridoxine; serenoa repens; tocopherol; zea mays; zinc allium sativum, latanoprost, probiotics nos, nicotinamide, buspirone, and ibuprofen The AE was reported 16 days after the 9th dose (received 14 donanemab doses total)
I5T-MC-AACG- (b) (6) PC	Small intestinal obstruction	73 M with PMH of AD, chronic kidney disease, enlarged prostate, seasonal allergy, psoriasis, sinus bradycardia, and eczema who was hospitalized for the SAE of small intestinal obstruction. The subject also experienced the following AEs on the same day: benign prostatic hyperplasia (severe), urinary retention (severe), bilateral hydronephrosis (severe), acute kidney injury (moderate), hypocalcemia (moderate), nausea (moderate), vomiting (moderate), and malnutrition (malnutrition). The subject underwent surgery 6 days later for bowel obstruction and was discharged from the hospital 9 days after surgery. At that time, the subject was considered to have recovered from the intestinal obstruction, hydronephrosis, and acute kidney injury. Concomitant medications: vitamins not otherwise specified. The AE was reported 15 days after the 4th donanemab dose (received 8 donanemab doses total)
I5T-MC-AACI- (b) (6) AP	Small intestinal obstruction	77 F with PMH of AD, hypothyroidism, hypertension, insomnia, who was hospitalized for abdominal pain and found to have on CT a small intestinal obstruction (moderate) in the right mid-abdomen of unknown cause. Temperature was 36.6 Celsius, heart rate 78, blood pressure 151/83, respirations 16 upon presentation. She was treated with metronidazole, ceftriaxone, morphine, ondansetron, promethazine, lohexol 300 and calcium chloride + potassium chloride + sodium lactate and discharged 3 days later. Surgery was not required. The subject was reported to have recovered from the small intestinal obstruction. Concomitant meds: aspirin, levothyroxine, losartan, metoprolol, memantine, donepezil, and nortriptyline. Risk factor: History of cholecystectomy and appendectomy. Nortriptyline may cause constipation.

USUBJID Pool	SAE	Comments
		The AE was reported 53 days after the 12 th donanemab dose (received 12 donanemab doses total)
I5T-MC-AACI- (b) (6) PC	Intestinal perforation	84 M who presented to the ER with on Study Day 136 with abdominal pain that had started that day, had a CT scan showed “right bowel perforation” and underwent exploratory laparotomy and right hemicolectomy the same day.⁶⁴ The subject was discharged on Study Day 141. Concomitant medications: levothyroxine, tamsulosin, mirtazapine, rivastigmine, memantine, naproxen, and multivitamin. Risk factors: PMH of small intestine ulcer and appendectomy, Constipation is one of the most common adverse reactions of mirtazapine and postmarketing intestinal obstruction has been reported. The AE was reported 23 days after 5th donanemab dose (received 6 donanemab doses total)
I5T-MC-AACI- (b) (6) PC	Large intestine perforation	77 M with past medical history of AD, hypertension, hyperlipidemia, BPH, chronic back pain, erectile dysfunction, neck neuropathy, depression, testicular hypofunction, back surgeries of repair of a ruptured disc, spinal decompression and cervical fusion, alcohol use, who was hospitalized for one month for an acute episode of severe diverticulitis with sepsis and colon perforation (severe) on Study Day 441. A partial colectomy and colostomy were performed within two weeks of hospitalization. Six months later, the colostomy was reversed and a loop ileostomy was performed. The ileostomy was reversed four months later. Concomitant meds: dexamethasone/neomycin/polymyxin B, amlodipine, atorvastatin, methocarbamol, oxycodone, lidocaine, acetaminophen, duloxetine, donepezil, memantine hydrochloride, silodosin, dutasteride, testosterone, mirtazapine, and potassium. Risk factors: Oxycodone has a contraindication for known or suspected gastrointestinal obstruction with a warning that includes postmarketing reports of intestinal obstruction and includes

⁶⁴ Noted in the Applicant’s response dated November 21, 2023, to an information request dated November 20, 2023.

USUBJID Pool	SAE	Comments
		constipation as one of the most common adverse reactions. Constipation is one of the most common adverse reactions of duloxetine. Constipation is one of the most common adverse reactions of mirtazapine and postmarketing intestinal obstruction has been reported. The AE was reported 55 days after 13 th dose (received 13 doses total)
I5T-MC-AACI- (b) (6) AP	Large intestine perforation	73 F who was hospitalized for perforated colon. An abscess was detected on CT scan. The subject was treated with intravenous antibiotics and ultimately underwent surgery. Concomitant medications: albuterol, atenolol, atorvastatin, dicyclomine, meloxicam, azelastine, fluticasone, vitamin D3, aspirin, escitalopram, memantine, and rivastigmine. Risk factors: PMH of irritable bowel syndrome, tubal ligation, and hysterectomy, and dicyclomine can cause constipation. The AE was reported 21 days after 1 st donanemab dose (received 6 donanemab doses total)

AP: all-donanemab pool. PC: placebo-controlled pool. PMH: past medical history

One additional serious case of intestinal obstruction was identified using the treatment period plus 57 days analysis method (I5T-MC-AACI- (b) (6)). This reviewer notes that the case appeared to be unrelated as the event occurred 155 days after the last dose of donanemab.

This reviewer notes one SAE of gastric obstruction (I5T-MC-AACI- (b) (6)). In this case, the cause of the gastric obstruction was suspected to be secondary to metastatic disease as findings on CT imaging also included severe right hydronephrosis secondary to right ureteropelvic junction obstruction, irregular soft tissue thickening along the renal pelvis, and irregular bladder wall thickening along the posterolateral aspect in the region of the right ureterovesical junction. The case had fatal outcome and is discussed further in the Deaths section of this review.

SAEs of Hernia

This reviewer identified 4 SAEs related to the topic of hernia, occurring in 4 subjects in the treatment period plus 57 days analysis method. Preferred terms included inguinal hernia (n=2), hiatus hernia and strangulated femoral hernia (one each).

In the placebo-controlled pool, three donanemab-treated subjects reported SAEs of hernia compared to one on placebo (0.3% versus 0.1%, respectively).⁶⁵

Two cases had preexisting hernias at the sites of the hernias as a risk factor (inguinal hernia, I5T-MC-AACI- (b) (6) and femoral hernia strangulation, I5T-MC-AACI- (b) (6)). A third subject had history of celiac artery stenosis, which may have been a contributory factor to the event of hernia (Hiatus hernia, I5T-MC-AACI- (b) (6)).

In the fourth case, this reviewer did not identify any risk factors that were contributory to the SAE of inguinal hernia (I5T-MC-AACI- (b) (6)). In this case, an 80 year-old subject with past medical history of AD, hypertension, dyslipidemia, benign prostatic hypertrophy, and normocytic anemia was admitted to the hospital for the SAE of inguinal hernia (moderate) and underwent surgery. He was discharged the following day. Concomitant medications included acetylsalicylic acid, doxazosin, atorvastatin, amlodipine and donepezil. The subject had no previous history of hernia or abdominal surgery.

TEAEs and SAEs related to Colitis

This reviewer identified eight TEAEs related to the topic of colitis reported in eight subjects in the all-donanemab pool. Preferred terms included microscopic colitis (n=3), clostridium difficile colitis, colitis, ischemic colitis, enterocolitis, and viral enterocolitis (one each).

Three of the cases were serious (Clostridium difficile colitis, I5T-MC-AACG- (b) (6) Colitis, I5T-MC-AACI- (b) (6); and microscopic colitis, I5T-MC-AACI- (b) (6)). In two of the three SAEs related to colitis, a role for donanemab could not be ruled out because of timing of the event and a lack of identifiable risk factors in the cases. One of the two cases involved a 67 year-old female subject who was diagnosed with lymphocytic colitis after undergoing an endoscopy while hospitalized for diarrhea (microscopic colitis, I5T-MC-AACI- (b) (6)). The SAE started 8 days after the 2nd donanemab infusion. Concomitant medications included rosuvastatin for this subject. Although rare cases of ischemic colitis have been reported with rosuvastatin⁶⁶ this reviewer considered it unlikely that the colitis was related to rosuvastatin, given that the subject had been on this medication for greater than 5 years. This reviewer did not identify any other concomitant medications that were contributory to risk for developing lymphocytic colitis.⁶⁷ The subject was treated with budesonide and at the time of the data

⁶⁵ Donanemab-treated participants with SAEs of hernia in the placebo-controlled pool: I5T-MC-AACI- (b) (6) I5T-MC-AACI- (b) (6), and I5T-MC-AACI- (b) (6)

⁶⁶ Tan J, Pretorius C, Flanagan P, et al. Adverse drug reaction: rosuvastatin as a cause for ischaemic colitis in a 64-year-old woman. BMJ Case Reports 2012;10.1136/bcr.11.2011.5270

⁶⁷ Other concomitant medications in this case included brimonidine eye drops, ciclosporin eye drops, levothyroxine, acetylsalicylic acid; caffeine; paracetamol PRN use, donepezil, and curcumin.

cutoff, the AE was ongoing and the symptom of diarrhea was improved. The subject received a third dose of donanemab 21 days later after the SAE at the time of the 90-Day cutoff. In the second of the two cases, the 81 year-old female subject with past medical history of diverticulitis developed symptoms of abdominal pain and vomiting and was hospitalized for acute right sided colitis on Day 130, 11 days after the 5th dose (Colitis, I5T-MC-AACI- (b) (6)). Per report, the diagnosis of colitis was based on laboratory details. Corrective treatment included iohexol, calcium chloride, potassium chloride, sodium lactate, ceftriaxone, metronidazole, and levofloxacin. No action was taken with study drug and the subject recovered on Day 132. Concurrent events in the case included identification of a mass in the right kidney, concerning for transitional cell cancer, while hospitalized. In the third case of colitis, a role for donanemab in the SAE of clostridium difficile colitis could not be established as the event occurred more than one year after the most recent dose of donanemab (clostridium difficile colitis, I5T-MC-AACG- (b) (6)). In this case the TEAE of ischemic colitis was also reported on the same day as the SAE of clostridium difficile colitis. This reviewer did not establish a role for donanemab in either the SAE of clostridium difficile colitis because of timing from the last dose of donanemab received ([I5T-MC-AACG- \(b\) \(6\)](#)).

This reviewer did not establish a role for donanemab in the remaining four TEAEs related to the topic of colitis. In one case, the subject had a history of inflammatory bowel disease and the symptom of diarrhea preceded the initial donanemab dose as a risk factor for microscopic colitis (microscopic colitis, I5T-MC-AACI- (b) (6)).⁶⁸ This subject also experienced the SAE of acute pancreatitis 8 days later, which is discussed in the [Serious Adverse Events](#) section of this review. In the second case with TEAE of microscopic colitis, a role for donanemab could not be established given concomitant ibuprofen use, which has been associated with colitis (I5T-MC-AACI- (b) (6)).⁶⁹ The reader is referred to the [Appendix](#) for further details of this case. In one of the cases with TEAE of enterocolitis, the subject had the concurrent AE of norovirus test positive, which was the likely cause for the enterocolitis (enterocolitis, I5T-MC-AACI- (b) (6)). The second case with TEAE of enterocolitis was attributed to a viral etiology (viral enterocolitis, I5T-MC-AACI- (b) (6)).

8.5.6. Safety Profile in No or Very Low Tau Burden Population

This reviewer did not identify a higher incidence of deaths, SAEs, or TEAEs in a population of subjects with no or very low tau burden as assessed by PET from Safety Addendum AACI compared to a population with low/medium or high tau burden as assessed by PET from the placebo-controlled period of AACI.

⁶⁸ Noted by the Applicant in a response dated December 5, 2023, to an information request dated December 4, 2023.

⁶⁹ Tonolini M. Acute nonsteroidal anti-inflammatory drug-induced colitis. J Emerg Trauma Shock. 2013 Oct-Dec; 6(4): 301–303.

doi: 10.4103/0974-2700.120389: 10.4103/0974-2700.120389

The safety profile of donanemab in a population of subjects with no or very low tau was of special interest because this population was excluded from the main study of AACI. The main study of AACI enrolled patients with low/medium or high tau burden as assessed by PET. The reader is referred to the review of clinical efficacy by Dr. Kevin Krudys for further details regarding inclusion criteria by tau burden as assessed by PET for the placebo-controlled period of AACI.

Safety Addendum AACI contained a subpopulation of subjects who were identified as having no or very low tau burden as assessed by PET (n=250) and formed the basis for the following analyses.

Comparator groups for the analyses in this section include the overall safety population of Safety Addendum AACI (n=1047) and donanemab-treated subjects in the placebo-controlled period of AACI (n=853). Similar to the no/very low tau burden population, subjects in both comparator groups had no prior exposure to donanemab. In the remaining population of subjects in Safety Addendum AACI (n=797), tau burden status as assessed by PET for these subjects was not known.⁷⁰ This reviewer notes that donanemab-treated subjects in the placebo-controlled period of AACI had low/medium or high tau burden as assessed by PET.

The no/very low tau burden population of AACI Safety Addendum was not observed to have a higher incidence of SAEs, TEAEs, TEAEs belonging to the SMQ of Anaphylactic Reaction/Hypersensitivity/Angioedema, ARIA, ARIA-E, ARIA-H, or intracerebral hemorrhage > 1 cm compared to the overall AACI Safety Addendum population or donanemab-treated subjects in the placebo-controlled period of AACI. The no/very low tau burden population did not have higher incidences of deaths or TEAEs reported to lead to study withdrawal and treatment discontinuation compared to the donanemab-treated population in the placebo-controlled period of AACI and had similar incidences compared to the overall population of AACI Safety Addendum (difference no greater than 2%). Limitations to this analysis include that the number of subjects with no or very low tau burden as assessed by PET was low (n=250). The following table shows incidence of TEAEs, deaths, SAEs, TEAEs reported to lead to study withdrawals or treatment discontinuations in the no/very low tau population of AACI Safety Addendum compared to the overall population of AACI Safety Addendum and the population in the placebo-controlled period of AACI.

⁷⁰ Noted by the Applicant in a response dated November 21, 2023, to an information request dated November 14, 2023.

Table 53. Overview of TEAEs in Donanemab-Treated Subjects (AACI Safety Addendum No/Very Low Tau Subpopulation, AACI Safety Addendum Overall Population, and the Placebo-Controlled Period of AACI populations)

	AACI Safety Addendum No/Very Low Tau Burden	AACI Safety Addendum Overall Population	Donanemab-treated Subjects in Placebo-Controlled Period of AACI
	Donanemab (N = 250) n (%)	Donanemab (N = 1047) n (%)	Donanemab (N = 853) n (%)
TEAEs	188 (75.2)	844 (80.6)	758 (88.9)
Deaths ^a	5 (2.0)	12 (1.1)	17 (2.0)
SAEs	31 (12.4)	142 (13.6)	140 (16.4)
TEAEs Reported to Lead to Study Withdrawal	14 (5.6)	45 (4.3)	67 (7.9)
TEAEs Reported to Lead to Treatment Discontinuation	22 (8.8)	84 (8.0)	111 (13.0)
TEAEs of the SMQs of Anaphylactic Reaction, Hypersensitivity, and Angioedema (Narrow)	29 (11.6)	151 (14.4)	132 (15.5)
Overview of ARIA ^b			
Any ARIA	66 (26.4)	311 (29.7)	307 (36.0)
Serious ARIA (-E or -H)	2 (0.8)	7 (0.7)	8 (0.9)
ARIA-E	43 (17.2)	206 (19.7)	201 (23.6)
Symptomatic ARIA-E	9 (3.6)	42 (4.0)	52 (6.1)
ARIA-H	55 (22.0)	254 (24.3)	263 (30.8)
Intracerebral hemorrhage > 1 cm	0	1 (0.1)	3 (0.4)

This table was created by Senior Clinical Analyst Dr. Rui Li and by this reviewer

^aIncidences of deaths are crude percentages and are based on an on-study approach.

^bIncidences of ARIA were based on analyses using the MRI dataset.

8.5.7. Suicide-related Events

This reviewer did not identify a safety signal for suicide-related events based on responses to the C-SSRS in the placebo-controlled pool and the all-donanemab pool and a review of narratives of suicide-related events.

The Applicant evaluated the incidence of positive responses to the Columbia Suicide Severity Rating Scale (C-SSRS) in the placebo-controlled pool and the all-donanemab pool and narratives

of suicide-related events. In the placebo-controlled period of Study AACI, the C-SSRS was administered at screening and during every study visit during the treatment period, the end of study visit.

Overall, this reviewer found the Applicant's approach for evaluation of suicide-related events to be acceptable.

A low incidence of suicide-related events with fatal outcome was observed in the placebo-controlled and all-donanemab pool. In the placebo-controlled pool, suicide-related events with fatal outcome was observed with similar incidence in the donanemab arm compared to placebo (0.2% [2/984] versus 0.1% [1/999], respectively). In the all-donanemab pool, suicide-related events with fatal outcome were observed in 0.1% (2/2802) of subjects.

In the two cases of suicide-related events with fatal outcome, this reviewer noted that the subject's had past medical history as potential contributory factors to the events of suicide ([I5T-MC-AACI-\(b\) \(6\)](#) and [I5T-MC-AACI-\(b\) \(6\)](#)).

This reviewer notes one additional serious case related to the topic of suicide. In this case, a role for donanemab was not established as the suicide attempt occurred greater than 150 days after the last dose of donanemab ([I5T-MC-AACI-\(b\) \(6\)](#)).

A similar incidence of suicidal ideation and suicidal behavior as assessed by the C-SSRS was observed in donanemab and placebo arms in the placebo-controlled pool (3.9% versus 4.5%, respectively). The following table shows C-SSRS responses for the placebo-controlled pool.

Table 54. C-SSRS Responses for the Placebo-controlled Pool

Responses	Donanemab (N = 978)	Placebo (N = 990)
Suicidal Ideation (1-5)	38 (3.9)	45 (4.5)
1. Wish to be Dead	33 (3.4)	39 (3.9)
2. Non-Specific Active Suicidal Thoughts	17 (1.7)	20 (2.0)
3. Active suicidal ideation with Any methods (Not Plan) without intent to Act	11 (1.1)	12 (1.2)
4. Active suicidal ideation with some intent to Act, without specific plan	0 (0.0)	5 (0.5)
5. Active suicidal ideation with specific plan and intent	1 (0.1)	3 (0.3)
Suicidal Behavior (6-10)	0 (0.0)	2 (0.2)
6. Preparatory Acts or Behavior	0 (0.0)	0 (0.0)

Responses	Donanemab (N = 978)	Placebo (N = 990)
7. Aborted Attempt	0 (0.0)	1 (0.1)
8. Interrupted Attempt	0 (0.0)	0 (0.0)
9. Actual Attempt (Non-Fatal)	0 (0.0)	2 (0.2)
10.Completed Suicide	0 (0.0)	0 (0.0)
Suicidal Ideation or Behavior (1-10)	38 (3.9)	45 (4.5)
Non-Suicidal Self Injurious Behavior	0 (0.0)	0 (0.0)

This table was created by Senior Clinical Analyst Dr. Rui Li.

A similar incidence of subjects with suicidal ideation and suicidal behavior was observed in the all-donanemab pool compared to the placebo-controlled pool (suicidal ideation: 3.4% versus 3.9%, respectively; suicidal behavior: 0.1% versus none, respectively).

In summary, this reviewer did not identify a safety signal for suicide-related events based on responses to the C-SSRS in the placebo-controlled pool and the all-donanemab pool and a review of narratives of suicide-related events.

8.6. Safety Analyses by Demographic Subgroups

In order to evaluate the effect of sex, age, race, region, ethnicity, and body mass index (BMI) on the safety of donanemab, this reviewer assessed incidences of most common TEAEs reported in the placebo-controlled period of AACI (ARIA-E, ARIA-H, infusion related reaction, superficial siderosis, and headache) in the specified demographic subgroups.

ARIA-E and headache were reported with higher incidence in subjects with lower BMI compared to higher BMI. A similar incidence of common TEAEs were observed in the demographic subgroups of sex, age group, and region. The number of subjects with race other than White, Hispanic or Latino ethnicity, and region other than North America or Europe was low and a conclusion regarding the impact of these demographic subgroups on the incidence of common adverse events cannot be drawn.

A similar incidence of the most common TEAEs was observed between female and male donanemab-treated subjects in the placebo-controlled period of AACI (difference no greater than 3%). The following table shows most common TEAEs in the placebo-controlled period of AACI by sex.

Table 55. Incidence of Common TEAEs by Sex in the Placebo-controlled Period of AACI

Preferred Term	Donanemab		Placebo	
	Male N=365 n (%)	Female N=488 n (%)	Male N=373 n (%)	Female N=501 n (%)
Amyloid related imaging abnormality- edema/effusion	84 (23.0)	120 (24.6)	10 (2.7)	7 (1.4)
Amyloid related imaging abnormality- microhemorrhages and hemosiderin deposits	74 (20.3)	96 (19.7)	23 (6.2)	41 (8.2)
Infusion related reaction	32 (8.8)	42 (8.6)	2 (0.5)	2 (0.4)
Superficial siderosis of central nervous system	28 (7.7)	26 (5.3)	6 (1.6)	4 (0.8)
Headache	45 (12.3)	70 (14.3)	27 (7.2)	59 (11.8)

This table was created by this reviewer using analyses by Senior Clinical Analyst Dr. Rui Li using the ADAE dataset.

A similar incidence of common TEAEs was observed between donanemab-treated subjects in the youngest age group and the oldest age group in the placebo-controlled period of AACI (difference no greater than 4%). The following table shows most common TEAEs in the placebo-controlled period of AACI by age group.

Table 56. Incidence of Common TEAEs by Age Group (Years) in the Placebo-controlled Period of AACI

Preferred Term	Donanemab			Placebo		
	<65 N=88 n (%)	≥65 - <75 N=414 n (%)	≥ 75 N=351 n (%)	<65 N=86 n (%)	≥65 - <75 N=402 n (%)	≥75 N=386 n (%)
Amyloid related imaging abnormality- edema/effusion	20 (22.7)	107 (25.8)	77 (21.9)	2 (2.3)	9 (2.2)	6 (1.6)
Amyloid related imaging abnormality- microhemorrhages and hemosiderin deposits	15 (17.0)	86 (20.8)	69 (19.7)	4 (4.7)	29 (7.2)	31 (8.0)
Infusion related reaction	10 (11.4)	37 (8.9)	27 (7.7)	0	1 (0.2)	3 (0.8)
Superficial siderosis of central nervous system	4 (4.5)	30 (7.2)	20 (5.7)	0	6 (1.5)	4 (1.0)
Headache	12 (13.6)	63 (15.2)	40 (11.4)	14 (16.3)	43 (10.7)	29 (7.5)

This table was created by this reviewer using analyses by Senior Clinical Analyst Dr. Rui Li using the ADAE dataset.

In the placebo-controlled period of AACI, races other than White had less than 100 subjects per arm, and a conclusion regarding the incidence of common AEs by race cannot be drawn. The

following table shows the incidence of common TEAEs by White and Asian race in the placebo-controlled period of AACI.

Table 57. Incidence of Common TEAEs by Race in the Placebo-controlled Period of AACI

Preferred Term	Donanemab		Placebo	
	White N=774 n (%)	Asian N=57 n (%)	White N=806 n (%)	Asian N=47 n (%)
Amyloid related imaging abnormality-edema/effusion	187 (24.2)	13 (22.8)	15 (1.9)	1 (2.1)
Amyloid related imaging abnormality-microhemorrhages and hemosiderin deposits	152 (19.6)	15 (26.3)	60 (7.4)	3 (6.4)
Infusion related reaction	68 (8.8)	3 (5.3)	4 (0.5)	0
Superficial siderosis of central nervous system	52 (6.7)	2 (3.5)	10 (1.2)	0
Headache	108 (14.0)	4 (7.0)	82 (10.2)	2 (4.3)

This table was created by this reviewer using analyses by Senior Clinical Analyst Dr. Rui Li using the ADAE dataset.

The number of subjects with Hispanic ethnicity in the placebo-controlled period of AACI was low (<50 subjects per arm) and a conclusion of the incidence of common TEAEs by ethnicity cannot be drawn. The following table shows the incidence of common TEAEs by ethnicity in the placebo-controlled period of AACI.

Table 58. Incidence of Common TEAEs by Ethnicity in the Placebo-controlled Period of AACI

Preferred Term	Donanemab		Placebo	
	Hispanic or Latino N=35 n (%)	Non-Hispanic or Latino N=806 n (%)	Hispanic or Latino N=37 n (%)	Non-Hispanic or Latino N=823 n (%)
Amyloid related imaging abnormality-edema/effusion	6 (17.1)	192 (23.8)	1 (2.7)	16 (1.9)
Amyloid related imaging abnormality-microhemorrhages and hemosiderin deposits	7 (20.0)	161 (20.0)	0	62 (7.5)
Infusion related reaction	2 (5.7)	71 (8.8)	1 (2.7)	3 (0.4)
Superficial siderosis of central nervous system	1 (2.9)	53 (6.6)	0	10 (1.2)
Headache	4 (11.4)	109 (13.5)	7 (18.9)	78 (9.5)

This table was created by this reviewer using analyses by Senior Clinical Analyst Dr. Rui Li using the ADAE dataset.

The number of subjects from the region of Japan in the placebo-controlled period of AACI was low (<50 subjects per arm) and a conclusion of the incidence of common TEAEs by the region of Japan cannot be drawn. A similar incidence of common TEAEs was reported in Europe compared to North America in donanemab-treated subjects (difference no greater than 4%). The following table shows the incidence of common TEAEs by North American and European regions in the placebo-controlled period of AACI.

Table 59. Incidence of Common TEAEs by Region in the Placebo-controlled Period of AACI

Preferred Term	Donanemab		Placebo	
	North America N=680 n (%)	Europe N=115 n (%)	North America N=703 n (%)	Europe N=124 n (%)
Amyloid related imaging abnormality-edema/effusion	163 (24.0)	25 (21.7)	14 (2.0)	2 (1.6)
Amyloid related imaging abnormality-microhemorrhages and hemosiderin deposits	132 (19.4)	26 (22.6)	47 (6.7)	14 (11.3)
Infusion related reaction	61 (9.0)	8 (7.0)	4 (0.6)	0
Superficial siderosis of central nervous system	46 (6.8)	6 (5.2)	9 (1.3)	1 (0.8)
Headache	99 (14.6)	13 (11.3)	64 (9.1)	21 (16.9)

This table was created by this reviewer using analyses by Senior Clinical Analyst Dr. Rui Li using the ADAE dataset.

ARIA-E and headache were reported with higher incidence in the lowest BMI tertile group compared to the highest BMI tertile group (ARIA-E: 27.8% versus 20.4% and Headache: 16.2% versus 10.7%, respectively). The following table shows the incidence of common TEAEs by BMI tertiles in the placebo-controlled period of AACI.

Table 60. Incidence of Common TEAEs by BMI (kg/m²) Tertiles in the Placebo-controlled Period of AACI

Preferred Term	Donanemab			Placebo		
	<23.5 N=277 n (%)	≥23.5 - <27.5 N=287 n (%)	≥ 27.5 N=289 n (%)	<23.5 N=312 n (%)	≥23.5 - <27.5 N=280 n (%)	≥27.5 N=282 n (%)
Amyloid related imaging abnormality-edema/effusion	77 (27.8)	68 (23.7)	59 (20.4)	2 (0.6)	8 (2.9)	7 (2.5)
Amyloid related imaging abnormality-	55 (19.9)	58 (20.2)	57 (19.7)	24 (7.7)	19 (6.8)	21 (7.4)

Preferred Term	Donanemab			Placebo		
	<23.5 N=277 n (%)	≥23.5 - <27.5 N=287 n (%)	≥ 27.5 N=289 n (%)	<23.5 N=312 n (%)	≥23.5 - <27.5 N=280 n (%)	≥27.5 N=282 n (%)
microhemorrhages and hemosiderin deposits						
Infusion related reaction	17 (6.1)	27 (9.4)	30 (10.4)	2 (0.6)	0	2 (0.7)
Superficial siderosis of central nervous system	16 (5.8)	18 (6.3)	20 (6.9)	3 (1.0)	3 (1.1)	4 (1.4)
Headache	45 (16.2)	39 (13.6)	31 (10.7)	30 (9.4)	28 (10.0)	28 (9.9)

This table was created by this reviewer using analyses by Senior Clinical Analyst Dr. Rui Li using the ADAE dataset.

8.7. Specific Safety Studies/Clinical Trials

Not applicable.

8.8. Additional Safety Explorations

8.8.1. Human Carcinogenicity or Tumor Development

This reviewer did not identify a safety signal for human carcinogenicity or tumor development in a review of TEAEs belonging to the SOC of Neoplasm in the placebo-controlled period of AACI, the placebo-controlled pool, or the all-donanemab pool. Analyses for detecting a safety signal for carcinogenicity were limited by the period of observation for subjects in the all-donanemab pool, where the median duration was less than 2 years.

A similar incidence of subjects reporting TEAEs belonging to the SOC of Neoplasm was observed in the donanemab and placebo arms of the placebo-controlled pool (7.0% versus 7.5%, respectively) and the placebo-controlled period of AACI (6.8% versus 7.2%, respectively). The following table shows TEAEs belonging to the SOC Neoplasm and occurring with higher incidence in the donanemab arm compared to placebo in the placebo-controlled pool.

Table 61. TEAEs Belonging to the SOC Neoplasm with Higher Incidence in the Donanemab Arm Compared to Placebo in the Placebo-controlled Pool.

Preferred Term	Donanemab N=984 n (%)	Placebo N=999 n (%)
Total Subjects with any TEAE within the SOC of Neoplasm	69 (7)	75 (7.5)
Cutaneous neoplasms benign	11 (1.1)	7 (0.7)
Seborrheic keratosis	6 (0.6)	2 (0.2)
Dysplastic naevus	2 (0.2)	0

Preferred Term	Donanemab N=984 n (%)	Placebo N=999 n (%)
Benign neoplasm of skin	1 (0.1)	0
Melanocytic naevus	3 (0.3)	3 (0.3)
Skin papilloma	0	2 (0.2)
Miscellaneous and site unspecified neoplasms malignant	15 (1.5)	12 (1.2)
Squamous cell carcinoma	15 (1.5)	11 (1.1)
Adenocarcinoma	0	1 (0.1)
Respiratory and mediastinal neoplasms benign	3 (0.3)	0
Benign lung neoplasm	2 (0.2)	0
Nasal neoplasm benign	1 (0.1)	0
Plasma cell neoplasms	3 (0.3)	1 (0.1)
Plasma cell myeloma	2 (0.2)	0
Monoclonal gammopathy	1 (0.1)	1 (0.1)
Skin neoplasms malignant	27 (2.7)	32 (3.2)
Basal cell carcinoma	20 (2)	19 (1.9)
Atypical fibroxanthoma	1 (0.1)	0
Malignant melanoma in situ	2 (0.2)	1 (0.1)
Bowen's disease	1 (0.1)	3 (0.3)
Keratoacanthoma	0	1 (0.1)
Skin cancer	0	1 (0.1)
Malignant melanoma	2 (0.2)	4 (0.4)
Squamous cell carcinoma of skin	2 (0.2)	5 (0.5)
Lymphomas non-Hodgkin's B-cell	1 (0.1)	1 (0.1)
B-cell lymphoma	1 (0.1)	0
Diffuse large B-cell lymphoma	0	1 (0.1)
Miscellaneous and site unspecified neoplasms benign	2 (0.2)	1 (0.1)
Benign neoplasm	1 (0.1)	0
Hemangioma	1 (0.1)	1 (0.1)
Renal and urinary tract neoplasms malignant	1 (0.1)	3 (0.3)
Bladder neoplasm	1 (0.1)	0
Bladder cancer	0	1 (0.1)
Bladder squamous cell carcinoma stage II	0	1 (0.1)
Bladder transitional cell carcinoma	0	1 (0.1)
Renal and urinary tract neoplasms benign	2 (0.2)	0
Bladder papilloma	1 (0.1)	0
Renal hamartoma	1 (0.1)	0
Breast neoplasms malignant and unspecified	3 (0.3)	5 (0.5)
Breast cancer	1 (0.1)	0

Preferred Term	Donanemab N=984 n (%)	Placebo N=999 n (%)
Breast neoplasm	1 (0.1)	0
Intraductal proliferative breast lesion	1 (0.1)	0
Breast cancer stage I	0	1 (0.1)
Invasive ductal breast carcinoma	1 (0.1)	1 (0.1)
Invasive lobular breast carcinoma	0	1 (0.1)
Metaplastic breast carcinoma	0	1 (0.1)
Mucinous breast carcinoma	0	1 (0.1)
Ocular neoplasms	2 (0.2)	1 (0.1)
Choroid melanoma	1 (0.1)	0
Choroidal hemangioma	1 (0.1)	0
Benign neoplasm of eyelid	0	1 (0.1)
Gastrointestinal neoplasms malignant	2 (0.2)	4 (0.4)
Lip squamous cell carcinoma	1 (0.1)	0
Pancreatic carcinoma	1 (0.1)	0
Adenocarcinoma pancreas	0	1 (0.1)
Lip neoplasm	0	1 (0.1)
Rectal cancer	0	2 (0.2)
Respiratory and mediastinal neoplasms malignant	2 (0.2)	2 (0.2)
Lung adenocarcinoma	1 (0.1)	0
Non-small cell lung cancer stage II	1 (0.1)	0
Lung adenocarcinoma stage IV	1 (0.1)	1 (0.1)
Lung neoplasm malignant	0	0.1
Hematopoietic neoplasms (excl leukemias and lymphomas)	1 (0.1)	0
Lymphoproliferative disorder	1 (0.1)	0
Gastrointestinal neoplasms benign	1 (0.1)	1 (0.1)
Pancreatic cystadenoma	1 (0.1)	0
Colorectal adenoma	0	1 (0.1)

This reviewer created this table using the 90-Day Safety IDB ADAE dataset, TEPCLDLFL, APERIODC = First Treatment Period, AESOC = Neoplasm.

This reviewer noted two serious cases with SOC of neoplasm in donanemab-treated subjects compared to none on placebo in the placebo-controlled pool (0.2% versus none, respectively). Both cases had preferred term of plasma cell myeloma (verbatim term: multiple myeloma: I5T-MC-AACI- (b) (6) and I5T-MC-AACI- (b) (6)). One case occurred on Study Day 78 and the other on Study Day 149. This reviewer did not establish a role for donanemab in the cases given the onset of the SAE from first exposure to donanemab.

In the all-donanemab pool at the 90-Day Safety Update, 4.9% of subjects reported at least one

TEAE belonging to the SOC of Neoplasms (138/2802). The preferred term with highest incidence in the all-donanemab pool was basal cell carcinoma (incidence of 1.7% [47/2802]).

Analyses to detect a safety signal for carcinogenicity are limited by the period of observation for subjects in the all-donanemab pool. This reviewer calculated the median duration of observation in the all-donanemab pool at the time of the 90-Day Safety Update to be 498.7 days (minimum: 3 days, maximum: 950 days).⁷¹

8.8.2. Human Reproduction and Pregnancy

There are no safety data on the use of donanemab in pregnant persons. The Applicant notes that pregnant persons were excluded from clinical studies. There were no reported instances of pregnancy or use during lactation in the development program.

8.8.3. Pediatrics and Assessment of Effects on Growth

Not applicable.

8.8.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

This reviewer did not identify a safety signal for overdose, abuse potential, withdrawal or rebound in a search of TEAEs related to these topics.

Overdose

This reviewer did not identify cases of overdose with donanemab in a search of TEAEs related to overdose in the all-donanemab pool.

The reviewer searched for TEAEs related to overdose in the all-donanemab pool at the 90-Day Safety Update

The reviewer did not identify any TEAEs related to overdose with donanemab. One subject in the all-donanemab pool was noted to have the TEAE of overdose with verbatim term insulin overdose (I5T-MC-AACI- (b) (6)). Three subjects were recorded as having been dispensed 2800 mg of donanemab at the same visit; however, the Applicant noted that in each of the cases, the subject did not receive more than planned dose.⁷² In two cases, additional study drug was dispensed because of incorrect drug preparation (I5T-MC-AACG- (b) (6) and I5T-MC-AACI- (b) (6) 171). In the third case, the subject had interruption of an infusion because of a presyncopal event, and the investigational product had to be dispensed two days later (5T-MC-

⁷¹ Observation time was based on the last disposition date noted in the ADDS file for a USUBJID (ADDS dataset, max ADY value). For the 90 subjects in the all-donanemab pool who did not have disposition dates in the ADDS dataset, observation time was estimated based on the study day for when the last dose of study drug was received (ADEX dataset, max ADY value).

⁷²Noted the Applicant's response dated November 8, 2022, to an information request dated November 7, 2022.

Clinical Review
Natalie Branagan, MD
BLA 761248
Kisunla/donanemab

AACI-256-90499).

The Applicant performed a similar search and did not identify a safety signal for overdose with donanemab.

Drug Abuse Potential

This reviewer did not identify a safety signal for drug abuse potential in a search of TEAEs related to abuse potential in the all-donanemab pool.

A consult with the Controlled Substance Staff (CSS) was not obtained for this review. Given that donanemab is anticipated to be given in a monitored setting, the anticipated risk for abuse appears to be low. In addition, abuse potential has not been identified with aducanumab or lecanemab, other amyloid-directed monoclonal antibody drugs.

The reviewer searched for TEAEs belonging to the SMQ Drug Abuse and Dependence and did not identify any TEAEs related to drug abuse potential with donanemab in the all-donanemab pool at the 90-Day Safety Update.

The Applicant performed a similar search and noted similar findings.

Withdrawal and Rebound

This reviewer did not identify a safety signal for withdrawal and rebound in a search of TEAEs belonging to the SMQ Drug Withdrawal.

One donanemab-treated subject reported a TEAE belonging to the SMQ of Drug Withdrawal compared to none on placebo in the placebo-controlled pool (0.1% [1/984] versus none [0/999], respectively). In this subject, the TEAE of drug withdrawal headache (mild) was reported in on Study Day 58, 28 days after the second dose of donanemab 700 mg (IST-MC-AACG- (b) (6)). The subject was reported to have ongoing mild asymptomatic ARIA-E (onset on Study Day 30, resolved Study Day 70) and ARIA-H superficial siderosis (onset Study Day 30, not covered/resolved at the time of study drug discontinuation). The study drug was discontinued per protocol discontinuation criteria of >1 treatment-emergent new area of superficial siderosis.

No additional TEAEs belonging to the SMQ of Drug Withdrawal were reported in the all-donanemab pool at the time of the 90-Day Safety Update.

8.9. Safety in the Postmarket Setting

8.9.1. Safety Concerns Identified Through Postmarket Experience

Not applicable. Donanemab is a new molecular entity. It is not approved in other regions of the

world.

8.9.2. Expectations on Safety in the Postmarket Setting

In clinical trials, donanemab was administered until amyloid reduction criteria were met. In the proposed label, no endpoints for ending dosing with donanemab are included. The risk of donanemab use in patients who meet amyloid reduction criteria used in clinical trials has not been assessed.

The population studied was relatively healthy, had mild cognitive impairment or mild AD. A low number of subjects with age < 65 years or age 85 years or older were enrolled. The risk of using donanemab in a population < 65 years of age or ≥85 years of age, a population with advanced comorbidities, or a population with more advanced stages of AD could be higher.

The population studied was predominantly White and not Hispanic or Latino. Due to the low number of subjects who were not of the White race or of Hispanic or Latino ethnicity, the safety of donanemab in these populations is unknown.

Patients with baseline MRIs that demonstrated presence of ARIA-E, > 4 cerebral microhemorrhages, more than 1 area of superficial siderosis, any macrohemorrhage or severe white matter disease were not studied. The safety profile of donanemab, including risk for ARIA and intracerebral hemorrhage, in these populations is unknown.

There are limited safety data related to continuing treatment with donanemab in patients who have experienced multiple episodes of ARIA-E. There is limited experience in continued dosing through symptomatic, radiographically mild ARIA-E that is allowed for in the approved label and that is the current class approach to dosing.⁷³

There are limited safety data in patients who received thrombolytics while on treatment with donanemab.

Subjects who experienced events of intracerebral hemorrhage > 1 cm while on treatment with donanemab did not receive additional doses of donanemab after the events of intracerebral hemorrhage. The safety of continued treatment with donanemab in patients who have experienced intracerebral hemorrhage > 1 cm while on donanemab therapy is unknown.

Assessments for human carcinogenicity were limited by the period of observation for subjects in the all-donanemab pool (median duration of ~500 days). The carcinogenic risk profile for donanemab with durations of treatment longer than what was studied is unknown.

⁷³ January 12, 2024, Response to information request.

The evaluation of safety in the placebo-controlled period of AACI and the placebo-controlled pool was limited by the percentage of subjects who withdrew from the study (approximately 27% of subjects in the donanemab arm and 20% on placebo in the placebo-controlled period of AACI and 27% and 21%, respectively, for the placebo-controlled pool). The analyses of safety may underestimate the incidence of adverse reactions with donanemab. However, of the subjects lost to follow-up, AEs at the last contact were not serious.

8.9.3. Additional Safety Issues From Other Disciplines

Not applicable.

8.10. Integrated Assessment of Safety

Safety findings from BLA 761248 are summarized below.

Relevant characteristics of the safety population. Patients with moderate or severe dementia were not included in AACG and AACI. Treatment was discontinued in clinical studies once subjects met criteria for amyloid plaque reduction. In the placebo-controlled period of AACI and the placebo-controlled pool, a low number of subjects were enrolled with the following demographic characteristics: age less than 65 years, age 85 years or older, non-White race, and Hispanic or Latino ethnicity. Conclusions regarding the impact of these demographic characteristics on the frequency of adverse events cannot be drawn.

Adequacy of the safety database. The safety database met ICH E1A guidelines for exposure of at least 300 subjects at 6 months and 100 subjects at 12 months at the proposed dose.

Deaths. In the placebo-controlled period of AACI, using the on study approach to evaluation, mortality at 76 weeks occurred in 2.2% (17/853) of subjects randomized to donanemab and in 1.2% (10/874) of subjects randomized to placebo, hazard ratio (95% CI) 1.79 (0.82, 3.93). Two deaths in the donanemab arm were attributed to ARIA. Intracerebral hemorrhage occurred in 1 subject with ARIA-H in the setting of findings that can be seen with cerebral amyloid angiopathy. In the all-donanemab pool, the incidence of deaths was 1.3%, with an additional death associated with ARIA and an additional death associated with intracerebral hemorrhage that occurred in a subject with ARIA-E, with symptoms mimicking stroke who was treated with thrombolytic therapy. There was no other unusual cluster of deaths in the database.

SAEs. A higher incidence of subjects reported SAEs in the donanemab arm compared to placebo in the placebo-controlled pool (16% versus 14%, respectively). ARIA-E and pneumonia were the SAEs reported with higher incidence in the donanemab arm compared to placebo and greatest difference in the placebo-controlled pool. ARIA-E was reported in 1.5% of subjects in the donanemab arm compared to none on placebo. Pneumonia was reported in 1% of subjects in the donanemab arm compared to 0.3% on placebo. In the all-donanemab pool, ARIA-E was the preferred term reported with highest incidence, occurring in 1.1% of subjects.

AEs Leading to Drug or Study Discontinuations. Approximately 26% of subjects in the donanemab arm and 20% on placebo withdrew from the study in the placebo-controlled period

of AACI. A higher incidence of donanemab-treated subjects reported adverse events leading to study withdrawal compared to placebo, occurring in 8% of subjects on donanemab versus 3% on placebo. Infusion related reaction, ARIA-E, and ARIA-H microhemorrhage were reported to lead to study withdrawal with highest incidence and greatest difference in donanemab-treated subjects compared to placebo in AACI. Adverse events lead to treatment discontinuation in 30% of donanemab-treated subjects compared to 20% on placebo in Study AACI. Infusion related reaction and ARIA-E were adverse events leading to treatment discontinuation with highest incidence in the donanemab arm and greatest difference from placebo in Study AACI.

Significant AEs. Evaluation of severe AEs did not identify a new safety signal.

Most Common AEs. ARIA-E, ARIA-H Microhemorrhage, ARIA-H Superficial Siderosis, infusion related reaction, and headache were TEAEs reported with highest incidence in the donanemab arm and greatest difference from placebo in the placebo-controlled period of AACI, occurring with incidence of at least 5% in the donanemab arm and at least 2% greater than placebo: ARIA-E (24% and 2% on donanemab and placebo, respectively), ARIA-H Microhemorrhage (25% and 11% on donanemab and placebo, respectively), ARIA-H Superficial Siderosis (15% and 3% on donanemab and placebo, respectively), infusion related reaction (9% and 0.5% on donanemab and placebo, respectively), and headache (13% and 10% on donanemab and placebo, respectively). AEs occurring in less than 5% of donanemab-treated subjects and at least 2% more than placebo in Study AACI included hypersensitivity reactions, intestinal obstruction, and intestinal perforation.

Vital sign, laboratory, and ECG evaluations in the placebo-controlled pool showed a slightly higher incidence of alkaline phosphatase ≥ 2 times the upper limit of normal in the donanemab arm compared to placebo (0.6% versus 0.2%).

Pre-specified AE of interest:

Hepatic Safety – An imbalance in alkaline phosphatase ≥ 2 times the upper limit of normal was observed in the placebo-controlled pool; however, the absolute difference in incidence between the donanemab and placebo arm was small (0.6% versus 0.2%, respectively). A review of narratives of subjects with hepatic enzyme elevation did not identify a safety signal for hepatotoxicity.

Immunogenicity - In the all-donanemab pool, 88% of subjects who were evaluable for treatment emergent anti-drug antibody (ADA) responses had a positive postbaseline treatment emergent ADA status. All of these subjects also had neutralizing antibody present.

ARIA – ARIA has been observed in other amyloid-directed monoclonal antibody therapies for the treatment of AD. In the placebo-controlled period of AACI, three cases of ARIA had fatal outcome. One additional fatal case of ARIA was observed in the all-donanemab pool. Serious ARIA-E cases were reported in 1.5% of subjects in the placebo-controlled period of AACI.

Symptomatic ARIA-E was reported in 6% of subjects in the placebo-controlled period of AACI. Intracerebral hemorrhage > 1 cm was reported in eight subjects (0.3%) in the all-donanemab pool.

Seizure – A higher incidence of seizure independent of ARIA was observed in donanemab-treated subjects compared to placebo in the placebo-controlled period of AACI (0.6% versus

0.3%, respectively). Seizure as a symptom of ARIA was reported in 0.6% of donanemab-treated subjects compared to none on placebo.

Hypersensitivity and infusion-related reactions – Infusion related reaction was reported in 8.7% of donanemab-treated subjects compared to 0.5% on placebo in Study AACI. Increases and decreases in blood pressure and increases in heart rate were observed in subjects with infusion related reactions. Hypersensitivity reactions, other than infusion related reactions, were reported in 2.9% of donanemab-treated subjects compared to 0.7% on placebo and included cases of anaphylaxis and angioedema.

Intestinal Obstruction or Intestinal Perforation – A higher incidence of donanemab-treated subjects reported intestinal obstruction compared to placebo in Study AACI (0.4%, based on three cases, versus none, respectively). A higher incidence of intestinal perforation was reported in donanemab-treated subjects compared to placebo in Study AACI (0.2% versus 0.1%, respectively). All of the cases were serious. A review of narratives of the cases demonstrated additional risk factors for obstruction or perforation, including concomitant medications or history of surgery.

Suicidality - There was no evidence of an increased risk of suicidality with donanemab.

9. Advisory Committee Meeting and Other External Consultations

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

For further information related to the topic of efficacy discussed at the AC meeting, please see the clinical review by Dr. Kevin Krudys.

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

10. Labeling Recommendations

10.1. Prescription Drug Labeling

This reviewer recommends a boxed warning be added to the USPI indicating that death occurring in patients with ARIA has occurred, which has been included in the labeling of other amyloid-directed antibodies. A higher incidence of deaths was observed in donanemab-treated subjects compared to placebo in the placebo-controlled period of AACI related to ARIA (1.7% versus 0.8%, respectively). The observed higher incidence was in part attributable to a higher incidence of fatal cases of death related to ARIA observed in the placebo-controlled period of AACI (0.2% in donanemab-treated subjects versus none on placebo). Excluding fatal cases of ARIA, the higher incidence of fatal cases were attributable to various other common conditions seen within an older population, including pneumonia, cerebrovascular accident, and dehydration.

This reviewer recommends that labeling include a Warnings and Precautions statements for ARIA, hypersensitivity reactions, and infusion related reactions. This reviewer recommends that increases and decreases in blood pressure observed in subjects with infusion reactions be described in the Warnings and Precautions statement for infusion related reactions.

This reviewer recommends that a statement regarding fatal cases of intracerebral hemorrhage occurring in the setting of thrombolytic administration be included in a Warnings and Precautions statement in labeling. Healthcare providers should be made aware that ARIA can present with focal neurologic symptoms that can mimic stroke. Patients who develop symptoms concerning for stroke may require a more extensive evaluation and MRI to assess the etiology of the symptoms. Patients should carry a medical information card indicating that they are being treated with donanemab and that donanemab can cause ARIA with symptoms that may mimic ischemic stroke. Healthcare providers should carefully consider the potential for ARIA and the potential benefits and risks when considering the use of a thrombolytic agent in a donanemab-treated patient with symptoms of stroke.

This reviewer recommends that a statement be included below the common adverse reactions table in labeling regarding the higher observed incidence of serious cases of intestinal obstruction and intestinal perforation.

This reviewer recommends that the incidence of donanemab-treated subjects with treatment emergent ADA responses, neutralizing antibodies, and infusion related reactions be included in the immunogenicity section of labeling.

10.2. Nonprescription Drug Labeling

Not applicable.

11. Risk Evaluation and Mitigation Strategies (REMS)

The Agency has determined that there is not a need for a REMS.

12. Postmarketing Requirements and Commitments

Postmarketing Requirements

Recommendations for postmarketing requirements:

The Applicant should conduct a registry-based, prospective, observational study to evaluate safety outcomes among Alzheimer's disease patients treated with donanemab, using, for example, the Alzheimer's Network for Treatment and Diagnostics (ALZ-NET) registry, including patients who are ApoE ϵ 4 homozygotes, and/or exposed to antithrombotics or thrombolytics, and/or have a diagnosis of, or imaging findings consistent with a high risk for, cerebral amyloid angiopathy. The primary clinical safety outcomes should include amyloid related imaging abnormalities (ARIA)-edema (ARIA-E), and ARIA hemosiderin deposition (ARIA-H) and any associated clinical symptoms, and intracerebral hemorrhage >1 cm in size. Additional outcomes of interest should also include seizures, anaphylaxis, and death.

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

Postmarketing Commitments

Recommendations for postmarketing commitments:

- The Applicant should conduct adequate analytical validation testing to establish and support labeling of an FDA cleared or approved in vitro diagnostic device to accurately and reliably detect ApoE ϵ 4 alleles that is safe and effective for identifying patients at increased risk of ARIA if treated with donanemab.

Pharmacovigilance

Recommendations for the Applicant for pharmacovigilance include:

- Expedited reporting of any deaths in ongoing studies and expedited reporting of events of intracerebral hemorrhage greater than 1 centimeter in size in ongoing studies or in the postmarketing setting.
- Perform postmarketing pharmacovigilance to characterize the risk of ARIA and the monitoring for ARIA associated with the use of donanemab. Provide biannual reports of ARIA-E and ARIA-H (specifying microhemorrhage or superficial siderosis), along with any incident intracerebral hemorrhage greater than 1 centimeter in size.
- Perform postmarketing pharmacovigilance to characterize the risk of hypersensitivity and infusion reactions associated with the use of donanemab.
- Perform postmarketing pharmacovigilance to characterize the risk of intestinal perforation and intestinal obstruction associated with the use of donanemab.

13. Appendices

13.1. EMQ/FMQ Groupings

The following is a list of preferred terms belonging to EMQ/FMQ Groupings in this review.

Allergic Reaction, Hypersensitivity

Anaphylactic reaction, anaphylactic shock, angioedema, conjunctivitis allergic, dermatitis allergic, dermatitis atopic, drug eruption, drug hypersensitivity, face edema, hypersensitivity, infusion related reaction, lip swelling, pharyngeal swelling, swelling face, and urticaria

Chest Pain (Non-cardiac or Unknown)

Chest discomfort, chest pain, musculoskeletal chest pain, and non-cardiac chest pain

Colitis, Gastroenteritis

Campylobacter infection, clostridium difficile colitis, colitis, colitis ischemic, colitis microscopic, colitis ulcerative, Crohn's disease, diarrhea, enteritis infectious, enterocolitis, enterocolitis viral, gastroenteritis, gastroenteritis viral, gastrointestinal infection, gastrointestinal viral infection, intestinal perforation, and large intestine perforation.

Fracture

Ankle fracture, avulsion fracture, cervical vertebral fracture, clavicle fracture, epiphyseal fracture, facial bones fracture, femoral neck fracture, femur fracture, fibula fracture, foot fracture, forearm fracture, fracture displacement, fractured sacrum, hand fracture, hip fracture, humerus fracture, jaw fracture, lower limb fracture, lumbar vertebral fracture, multiple

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fractures, osteoporotic fracture, patella fracture, pelvic fracture, periprosthetic fracture, radius fracture, rib fracture, scapula fracture, spinal compression fracture, spinal fracture, sternal fracture, stress fracture, thoracic vertebral fracture, tibia fracture, ulna fracture, upper limb fracture, and wrist fracture.

Gastritis, Duodenitis

Chronic gastritis, duodenitis, dyspepsia, gastric polyps, gastritis, gastritis erosive, helicobacter gastritis, nausea, procedural nausea, procedural vomiting, and vomiting.

Infection

Abscess, abscess limb, abscess oral, acute sinusitis, appendicitis, appendicitis perforated, arthritis bacterial, atypical pneumonia, bacterial infection, bacterial sepsis, bronchitis, bronchitis viral, campylobacter infection, cellulitis, cholecystitis, cholecystitis acute, cholecystitis chronic, chronic sinusitis, clostridium difficile colitis, clostridium difficile infection, cystitis, cytomegalovirus infection, dacryocystitis, dermatitis infected, dermatophytosis of nail, diverticulitis, ear infection, enteritis infectious, enterococcal bacteremia, enterocolitis viral, escherichia infection, escherichia sepsis, escherichia urinary tract infection, eye infection, eye infection bacterial, eyelid infection, folliculitis, fungal infection, fungal esophagitis, fungal skin infection, furuncle, gastroenteritis, gastroenteritis viral, gastrointestinal infection, gastrointestinal viral infection, gingival abscess, helicobacter gastritis, helicobacter infection, herpes simplex, herpes zoster, hordeolum, infected bite, infected dermal cyst, infection, influenza, influenza like illness, kidney infection, labyrinthitis, laryngitis, laryngitis viral, localized infection, lower respiratory tract infection, lyme disease, mastitis, nasopharyngitis, esophageal candidiasis, onychomycosis, ophthalmic herpes simplex, oral candidiasis, oral fungal infection, oral herpes, oral infection, orchitis, osteomyelitis, otitis externa, otitis media, otitis media acute, overgrowth fungal, pelvic abscess, periorbital cellulitis, peritoneal abscess, peritonitis, pertussis, pharyngitis, pharyngitis bacterial, pharyngitis streptococcal, pneumonia, pneumonia aspiration, pneumonia bacterial, pneumonia klebsiella, pneumonia legionella, post procedural cellulitis, post procedural infection, postoperative wound infection, prostate infection, pulpitis dental, pyelonephritis, respiratory tract infection, rhinitis, rhinovirus infection, salmonellosis, scrotal infection, sepsis, sialoadenitis, sinobronchitis, sinusitis, skin infection, staphylococcal abscess, staphylococcal bacteremia, staphylococcal infection, staphylococcal skin infection, streptococcal urinary tract infection, subcutaneous abscess, testicular abscess, tinea cruris, tinea infection, tinea pedis, tooth abscess, tooth infection, upper respiratory tract infection, upper respiratory tract infection bacterial, urinary tract infection, urinary tract infection bacterial, urinary tract infection pseudomonal, urosepsis, vaginal infection, viral infection, viral pharyngitis, viral rhinitis, viral upper respiratory tract infection, vulvovaginal candidiasis, vulvovaginal mycotic infection, and wound infection.

Intracranial Hemorrhage

Cerebral hematoma, cerebral hemorrhage, cerebral microhemorrhage, extradural hematoma, hemorrhage intracranial, hemorrhagic stroke, intraventricular hemorrhage, subarachnoid hemorrhage, subdural hematoma, subdural hemorrhage, and thalamus hemorrhage.

13.2. Exposure Calculation by Applicant

At the time of the 90-Day Safety Update, the Applicant calculated 1,678 subjects with at least 6 months of exposure and 964 subjects with at least 12 months of exposure in the all-donanemab pool. The Applicant included only subjects who received 700 mg as their first three doses followed by 1400 mg for the remaining doses, which led to a lower number of subjects in the exposure counts compared to the Division's method. The Division's method included subjects who received 1400 mg for the first 3 doses prior to the protocol amendment that changed the first three doses to 700 mg. The Division's method also included subjects who received less than or more than three 700 mg doses, although no more than three 700 mg doses were counted in the exposure calculations for each subject.^{74,75}

13.3. Baseline Demographics for the Pooled Placebo-Controlled Studies

The following table shows baseline demographics for the pooled placebo-controlled studies.

Table 62. Baseline Demographics for the Pooled Placebo-Controlled Studies

Parameter	Donanemab N=984	Placebo N=999	Total N=1983
Sex			
Female	556 (56.5)	565 (56.6)	1121 (56.5)
Male	428 (43.5)	434 (43.4)	862 (43.5)
Age			
Mean (SD)	73.2 (6.1)	73.3 (6.1)	73.3 (6.1)
Median (Min, Max)	73 (59, 86)	74 (59, 85)	74 (59, 86)
Age Group (years)			
<65	93 (9.5)	91 (9.1)	184 (9.3)
>=65 and <75	469 (47.7)	448 (44.8)	917 (46.2)
>=75 and <85	402 (40.9)	444 (44.4)	846 (42.7)
>=85	20 (2)	16 (1.6)	36 (1.8)

⁷⁴Noted by the Applicant in a response dated September 1, 2023, to an information request dated August 31, 2023.

⁷⁵This reviewer notes that in the all-donanemab pool, there were 2,031 participants who were exposed to at least 6 doses of donanemab *at any dose* and 1,138 participants with 12 doses of donanemab *at any dose* at the time of the 90-Day Safety Update per analyses performed by Senior Clinical Analyst Dr. Rui Li.

Parameter	Donanemab N=984	Placebo N=999	Total N=1983
Race			
American Indian or Alaska Native	4 (0.4)	0	4 (0.2)
Asian	58 (5.9)	49 (4.9)	107 (5.4)
Black or African American	24 (2.4)	23 (2.3)	47 (2.4)
Multiple	1 (0.1)	1 (0.1)	2 (0.1)
White	896 (91.1)	926 (92.7)	1822 (91.9)
Ethnicity			
Hispanic	40 (4.1)	40 (4)	80 (4)
Not Hispanic or Latino	932 (94.7)	945 (94.6)	1877 (94.7)
Not reported	11 (1.1)	12 (1.2)	23 (1.2)
Country			
Australia	13 (1.3)	4 (0.4)	17 (0.9)
Canada	73 (7.4)	84 (8.4)	157 (7.9)
Czech Republic	12 (1.2)	10 (1)	22 (1.1)
United Kingdom	15 (1.5)	23 (2.3)	38 (1.9)
Japan	45 (4.6)	43 (4.3)	88 (4.4)
Netherlands	12 (1.2)	9 (0.9)	21 (1.1)
Poland	76 (7.7)	82 (8.2)	158 (8)
United States	738 (75)	744 (74.5)	1482 (74.7)
ApoE ε4 carrier status ^a			
Heterozygote	522 (53)	538 (53.9)	1060 (53.5)
Homozygote	168 (17.1)	174 (17.4)	342 (17.2)
Non-Carrier	291 (29.6)	282 (28.2)	573 (28.9)
Unknown	3 (0.3)	5 (0.5)	8 (0.4)
Disease Severity Status at Baseline			
MCI (MMSE>26)	171 (17.4)	159 (15.9)	330 (16.6)
Mild (20<=MMSE<=26)	801 (81.4)	831 (83.2)	1632 (82.3)
Moderate (MMSE<20)	7 (0.7)	4 (0.4)	11 (0.6)
No baseline or screening MMSE	5 (0.5)	5 (0.5)	10 (0.5)
Baseline BMI (kg/m ²)			
Mean (SD)	26 (4.9)	25.8 (4.7)	25.9 (4.8)
Median (Min, Max)	25.6 (13, 47.4)	25.3 (15.9, 49.4)	25.4 (13, 49.4)

BMI: Body mass index. MCI: mild cognitive impairment. MMSE: Mini-Mental Status Examination. The reviewer created this table using IDB ADSL, PCSAFL = Y.

^aOf note, the denominator used in labeling among donanemab-treated subjects was 981 based on the 3 subjects who had missing ApoE ε4 status leading to incidences of 53%, 17%, and 30% for heterozygotes, homozygotes, and non-carriers, respectively.

13.4. Issues Regarding Data Integrity and Submission Quality

The 90-Day Safety Update did not contain a re-analysis of the placebo-controlled pool to include events occurring in 10 subjects who were ongoing in the placebo-controlled period of Study AACI at the time of the resubmission. The database for Study AACI did not reflect the most recent information regarding disposition events related to study and treatment for three subjects in the placebo-controlled period of Study AACI. Duplication of adverse events occurred in two subjects from Study AACI because of differences in categorization of the seriousness of the events. Two subjects from Study AACI had missing reference range laboratory values. Differences in the number of adverse events in the SDTM and ADAM datasets from the integrated database were attributed to the SDTM dataset including adverse events occurring in subjects exposed to donanemab in combination with a BACE1 inhibitor. Differences in treatment emergent status between datasets were attributed to differences in definitions of events that were considered baseline events or to imputation of an event as treatment emergent if data related to the onset of the event was missing.

At the time of the resubmission, the Division noted 10 subjects had an ongoing status for the placebo-controlled period of Study AACI.⁷⁶ Because of the ongoing status of the 10 subjects at the time of the resubmission, the Division requested that the Applicant submit updated analyses for the placebo-controlled pool, which had not been included in the 90-Day Safety Update.⁷⁷

On October 11, 2023, the Division extended the goal date by three months to allow for further review of the Applicant's submissions, which constituted a major amendment for the application (dates of submissions: July 31, 2023, September 5, 2023, and October 10, 2023).

In the Applicant's submission dated October 10, 2023, the Division noted four subjects from the placebo-controlled period of AACI with ongoing status.⁷⁸ A response dated October 19, 2023, to an information request dated October 19, 2023, the Applicant indicated that one of the subjects discontinued the study the week following the data cutoff for the 90-Day Safety Update (IST-MC-AACI- (b) (6)). For two subjects, the Applicant indicated that the database

⁷⁶ Noted on page 183 of the RISS (Table R-ISS.6.6) of the Applicant's resubmission dated June 12, 2023.

⁷⁷ Analyses of data from the placebo-controlled pool after the 90-Day Safety Update submitted by the Applicant on October 10, 2023, in response to an information request dated October 2, 2023.

⁷⁸ Noted on pages 18 (Table APP.1) and 21 (Table APP.2) of the Applicant's response dated October 10, 2023, to an information request dated October 2, 2023.

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had not been updated to indicate the subjects had withdrawn from the study (I5T-MC-AACI- (b) (6) and I5T-MC-AACI- (b) (6)). For the remaining subject, the Applicant noted that that the subject had been lost to follow-up (I5T-MC-AACI- (b) (6)).

Reviewer comment: This reviewer notes adverse events occurring in the subject who discontinued after the 90-Day Safety cutoff date would be unlikely attributed to donanemab given the length of time since receipt of the last dose of donanemab (I5T-MC-AACI- (b) (6)). The subject had received donanemab and then had been switched to placebo and had received at least 9 infusions of placebo at the time of the 90-Day Safety cutoff date.

SDTM to ADAM and individual study ADAM to the integrated database ADAM traceability assessments were performed by the Office of Computational Science.

Two individuals from Study AACI were noted to have duplication of adverse events related to differences in qualifying the seriousness of the event (fracture of the lumbar spine, I5T-MC-AACI- (b) (6) and fainting, I5T-MC-AACI- (b) (6)).⁷⁹ Overall, this reviewer noted that assessments of the incidence of adverse events calculated on a per subject basis would not be affected by the duplication of these events.

Additionally, reference ranges for laboratory values were missing for two subjects in Study AACI (I5T-MC-AACI- (b) (6) and I5T-MC-AACI- (b) (6)). The Applicant acknowledged that these ranges were inadvertently missing and provided reference range values for these subjects.⁸⁰

Some subjects had adverse events noted in the adverse event SDTM dataset that were not included in the ADAM datasets for Study AACI (I5T-MC-AACI- (b) (6) covid-19 [start date (b) (6)], large intestinal polyp, and diarrhea; I5T-MC-AACI- (b) (6) hypotension and agitation; and I5T-MCAACI- (b) (6) urinary tract infection [start date (b) (6)] and agitation). The Applicant noted only adverse events occurring in the double-blind analysis period of the study (end date of the period defined as either the first visit date of the long-term extension phase -1 day or the end of the treatment period in the double blinded phase + 57 days, whichever occurred first) were included in the AACI ADAM datasets.⁸¹ The reviewer notes that analyses of events occurring in the long-term extension period of Study AACI in this review used the adverse event dataset from the integrated database; therefore, analyses of events in the long-term extension period were not affected by Study AACI datasets.

Some subjects had adverse events noted in the SDTM dataset that were not included in the ADAM datasets for the integrated database (I5T-MC-AACG- (b) (6): amyloid related imaging abnormality-edema/effusion; I5T-MC-AACG- (b) (6): procedural anxiety; and I5T-MC-AACG-

⁷⁹ Noted in a response dated July 24, 2023, to an information request dated July 21, 2023.

⁸⁰ Noted in a response dated July 24, 2023, to an information request dated July 21, 2023.

⁸¹ Noted in a response dated July 24, 2023, to an information request dated July 21, 2023.

(b) (6) infusion related reaction). The Applicant noted that adverse events occurring in subjects exposed to donanemab in combination with a BACE1 inhibitor were included in the SDTM dataset but not in the ADAM dataset.⁸² The reviewer notes that adverse events occurring subjects exposed to the combination therapy were previously evaluated in this reviewer's Clinical Review of Safety for the initial donanemab submission dated January 17, 2023.

This reviewer noted three subjects who had adverse events with different treatment emergent statuses between different datasets. For two subjects, the Applicant indicated that differences in treatment emergent status were due to differences in definitions of baseline event.⁸³ For subject I5T-MC-AACG-(b) (6) standardized term: Squamous cell carcinoma, an event in the integrated database was considered a baseline event if the event was ongoing at the time of the first dose. In the SUPPAE dataset for Study AACH, an event was considered a baseline event if had started prior to the first dose, regardless of whether the event was ongoing at the time of the first dose. In the second subject, I5T-MC-AACI-(b) (6) the preferred term Blood Bilirubin Increased was flagged as treatment emergent in the AACI dataset but not in the integrated database. This subject had a medical history of Blood Bilirubin Increased with end date on the same day as the subject's informed consent. In Study AACI, an event was considered a baseline event if the event occurred prior to the informed consent date, whereas in the integrated database, an event was considered a baseline event if it occurred before or on the date of informed consent. In the third subject, I5T-MC-AACG-(b) (6) standardized term: Metabolic encephalopathy, the event start date was missing. In the SUPPAE dataset, missing data was not imputed and the event was not considered treatment emergent; however, in the integrated database, the Applicant indicated that such events were considered to be treatment emergent to be conservative.

Overall, this reviewer found the Applicant's explanations for differences in treatment emergent status between datasets to be acceptable.

Of note, the Applicant's calculations for adverse events for Study AACI differed from the pooled placebo-controlled trials and the all-donanemab pool because the Applicant's calculations for Study AACI included adverse events that occurred after the screening visit and before the first dose. Calculations for the placebo-controlled pool and the all-donanemab pool used the integrated database and included only adverse events occurring after the subject had received study drug.⁸⁴ For example, the following subjects experienced adverse events after the screening visit and prior to the first dose and were included in summaries of adverse events for Study AACI, but not in the placebo-controlled or all-donanemab pools: I5T-MC-AACI-(b) (6) /SAE of Covid-19, I5T-MC-AACI-(b) (6) and I5T-MC-AACI-(b) (6) /SAEs of syncope, and I5T-MC-AACI-(b) (6) /AE of meningioma reported to lead to treatment discontinuation.

⁸² Noted in a response dated July 24, 2023, to an information request dated July 21, 2023.

⁸³ Noted in a response dated July 24, 2023, to an information request dated July 21, 2023.

⁸⁴ Noted in a response dated August 28, 2023, to an information request dated August 25, 2023.

13.5. Routine Clinical Tests

In the placebo-controlled and long-term extension periods of Study AACI, vital signs, including blood pressure, pulse, and temperature, were measured at baseline and at all visits during treatment periods and during follow up periods. Orthostatic blood pressure and pulse, taken after 5 minutes in the supine position and after at least 3 minutes of standing, was measured at Weeks 0, 12, 24, 36, 52, 64, 76, the Early Discontinuation visit, and unscheduled visits. Laboratory tests included hematology and clinical chemistry tests were collected prior to IP dosing and at baseline, Weeks 0, 12, 24, 36, 52, 64, 76, and the Early Discontinuation visit. Urine analyses were measured at Weeks 0, 24, 76, and the Early Discontinuation visit. ECGs were measured at baseline, Weeks 0, 24, 52, 76, and the Early Discontinuation visit. ECGs were interpreted by a physician at the study site and then were read at a central ECG laboratory by a cardiologist.

In Study AACN Dona-Cohort, vital signs were measured prior to and within 30 minutes after infusion for clinical management. Laboratory tests included hematology and clinical chemistry tests were collected at baseline, Weeks 24, 52, 76, and Early Termination visit. A single, locally-read ECG was performed at screening.

For studies AACG, AACI Safety Addendum, AACH Part B, and AACN-Dona Cohort, this reviewer found the safety assessment methods and timepoints to be adequate for the safety review. The reader is referred to this reviewer's Safety Review dated January 17, 2023, for further details on the methods of routine clinical tests for these studies.

13.6. Deaths in the Placebo-controlled Pool and the All-Donanemab Pool

The following table shows the incidence of adverse events with fatal outcome in the placebo-controlled pool at Week 76.

Table 63. Incidence of Adverse Events with Fatal Outcome in the Placebo-Controlled Pool at Week 76^a

Preferred Term	Donanemab (N = 984)	Placebo (N = 999)
Subjects with Fatal Adverse Events	18 (1.8%)	11 (1.1%)
Pulmonary embolism	2 (0.2%)	0 (0.0%)
Amyloid related imaging abnormality-edema/effusion ^b	1 (0.1%)	0 (0.0%)
(ARIA-E) and Amyloid related imaging abnormality-microhemorrhages and hemosiderin deposits (ARIA-H) ^c	1 (0.1%)	0 (0.0%)

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Preferred Term	Donanemab (N = 984)	Placebo (N = 999)
Intracerebral hemorrhage ^d	1 (0.1%)	0 (0.0%)
COVID-19	1 (0.1%)	0 (0.0%)
Dehydration	1 (0.1%)	0 (0.0%)
Respiratory arrest	1 (0.1%)	0 (0.0%)
Respiratory failure	1 (0.1%)	0 (0.0%)
Retroperitoneal hemorrhage	1 (0.1%)	0 (0.0%)
Subarachnoid hemorrhage	1 (0.1%)	0 (0.0%)
Completed suicide	2 (0.2%)	1 (0.1%)
Pneumonia	2 (0.2%)	2 (0.2%)
COVID-19 pneumonia ^e	1 (0.1%)	1 (0.1%)
Death	1 (0.2%)	1 (0.1%)
Dementia Alzheimer's type	1 (0.1%)	1 (0.1%)
Arteriosclerosis	0 (0.0%)	1 (0.1%)
Cardiac arrest	0 (0.0%)	1 (0.1%)
Myocardial infarction	0 (0.0%)	1 (0.1%)
Respiratory fume inhalation disorder	0 (0.0%)	1 (0.1%)
Sepsis	0 (0.0%)	1 (0.1%)

The reviewer created this table using the 90DaySafety Update IDB ADAE dataset, DTHAEFL = Yes, STUDYID = AACI, APERIODC = First treatment period or missing, AEENDY = ≤ 532 and USUBJID from ADSL not equal to AACIA9FL = Y and ISAFFL = Y.

^aPercentages are based on crude percentages.

^bI5T-MC-AACI- (b) (6)

^cSubject I5T-MC-AACI- (b) (6) with preferred term of “death.” The events associated with death were ARIA-E and ARIA-H.

^dI5T-MC-AACI- (b) (6) intracerebral hemorrhage in the setting of ARIA-E and ARIA-H, with superficial siderosis at baseline

^eThis includes I5T-MC-AACI- (b) (6) with preferred term of respiratory failure, which occurred in the setting of COVID-19 pneumonia.

The following table shows the incidence of adverse events with fatal outcome in the all-donanemab pool using an on-study approach.

Table 64. Incidence of Adverse Events with Fatal Outcome in the All-Donanemab Pool, On Study Approach

Preferred Terms	Donanemab (N =2802)
Subjects with Fatal Adverse Events	37 (1.3%)
Pneumonia ^a	3 (0.1%)
Respiratory failure ^b	3 (0.1%)
Death	2 (0.1%)
Amyloid related imaging abnormality-edema/effusion ^c	2 (0.1%)
(ARIA-E) and Amyloid related imaging abnormality-microhemorrhages and hemosiderin deposits (ARIA-H) ^d	1 (0.0%)
Completed suicide	2 (0.1%)
Dehydration	2 (0.1%)
Pulmonary embolism	2 (0.1%)
Intracerebral hemorrhage ^e	2 (0.1%)
Aortic dissection	1 (0.0%)
COVID-19	1 (0.0%)
COVID-19 pneumonia	1 (0.0%)
Cardiac arrest	1 (0.0%)
Cardiac failure congestive	1 (0.0%)
Dementia Alzheimer's type	1 (0.0%)
Dementia with Lewy bodies	1 (0.0%)
Gun shot wound	1 (0.0%)
Head injury	1 (0.0%)
Metabolic encephalopathy	1 (0.0%)
Myocardial infarction	1 (0.0%)
Pancreatic carcinoma metastatic	1 (0.0%)
Pelvic fracture	1 (0.0%)
Renal failure	1 (0.0%)

Preferred Terms	Donanemab (N =2802)
Respiratory arrest	1 (0.0%)
Retroperitoneal hemorrhage	1 (0.0%)
Subarachnoid hemorrhage	1 (0.0%)
Thalamus hemorrhage	1 (0.0%)

The above table was created by this reviewer using the ADAE dataset.

^aIncludes aspiration pneumonia.

^bIncludes acute respiratory failure.

^cI5T-MC-AACI- (b) (6) and I5T-MC-AACI- (b) (6)

^dSubject I5T-MC-AACI- (b) (6) with the preferred term of “death.” The events associated with death were ARIA-E and ARIA-H.

^eThis includes I5T-MC-AACI- (b) (6) who had intracerebral hemorrhage in the setting of ARIA-E and ARIA-H, with superficial siderosis at baseline and I5T-MC-AACI- (b) (6) who reported the preferred term of hemorrhage intracranial.

13.7. Additional Narratives of Deaths

The following section contains narratives of deaths, excluding deaths related to ARIA and intracerebral hemorrhage, which are included in the Deaths section of this review.

Details for narratives were taken from the donanemab resubmission dated June 12, 2023, and from the initial submission dated May 18, 2022. The following additional topics were identified when grouping cases for review of narratives: intracerebral hemorrhage, cerebral infarction/cerebral ischemia, pneumonia, dehydration, pulmonary embolism, respiratory failure, suicide, and trauma.

Fatal Outcomes Related to the Topic of Intracerebral Hemorrhage

Because fatal events of intracerebral hemorrhage have been reported with other amyloid-directed monoclonal antibody drugs, the topic of intracerebral hemorrhage was of special interest.^{85,86}

Narratives for three cases of intracerebral hemorrhage are in the Deaths section of this review:

[I5T-MC-AACI- \(b\) \(6\)](#) [I5T-MC-AACI- \(b\) \(6\)](#) and [I5T-MC-AACI- \(b\) \(6\)](#)

In a remaining case of subarachnoid hemorrhage, likely contributory factors included the

⁸⁵ Aduhelm. Labeling-Prescribing Information. Drugs@fda.gov. Action date February 8, 2023. Accessed August 25, 2023.

⁸⁶ Leqembi. Labeling-Prescribing Information. Drugs@fda.gov. Action date July 6, 2023. Accessed August 24, 2023.

preceding event of fall from a ladder, as well as the subject's past medical history of falls, unsteadiness, and concomitant acetylsalicylic acid use (subarachnoid hemorrhage, I5T-MC-AACI- (b) (6)). The last dose of donanemab (6th dose) had been 75 days prior to the event.

Fatal Outcomes related to Cerebral Infarction/Cerebral Ischemia

One case was identified that was related to the topic of cerebral infarction/cerebral ischemia (I5T-MC-AACI- (b) (6)). In this case, the subject developed cerebral infarction during hospitalization for Covid-19 pneumonia. This reviewer did not identify a role for donanemab in the event of cerebral infarction because of the concurrent event of atrial fibrillation, which was a potential risk factor. The case is summarized here.

Covid-19 pneumonia, I5T-MC-AACI- (b) (6)

An 82 year-old male subject with past medical history of chronic obstructive pulmonary disease, asthma, chronic bronchitis, diabetes mellitus type 2 with nephropathy, aortic valve stenosis, congestion heart failure, hypertension, hyperlipidemia, unvaccinated status for Covid-19, ApoE ε3/ε4 carrier, dementia, who presented to the ER with shortness of breath and hypertension and was hospitalized for Covid-19 pneumonia on Study Day 77. The SAE occurred 22 days after the 3rd dose. The subject had tested positive for Covid-19 on Study Day 70 and had reported symptoms starting 5 days prior to the positive Covid-19 test. The subject became confused, agitated, and reported hallucinations. He was noted to be hypoxic upon arrival (vitals not reported) and was placed on oxygen. The CBC was reported to be unremarkable and a chest x-ray showed bilateral infiltrates. He was treated with IV fluids, dexamethasone, and placed on BIPAP. The following day, he was transferred to another hospital because of lack of bed space. Admitting diagnoses at the second hospital were reported to be cardio, Covid-19 pneumonia with acute respiratory distress syndrome, non-ST-elevation myocardial infarction, new onset atrial fibrillation. He was noted to have decompensated rapidly and required rapid sequence intubation. Corrective treatments were reported to include etomidate, propofol, norepinephrine, fentanyl, remdesivir, insulin and alteplase (2 mg IV prn from Study Day 78 to 85).⁸⁷ On the same day, he was found to have a deep vein thrombosis in the lower leg and was placed on a heparin drip. He remained on the ventilator, developed acute kidney insufficiency. He was noted to remain encephalopathic despite decreasing sedation to wean from ventilator. A CT of the head on Study Day 81 showed nonspecific periventricular white matter hypodensities, possibly representing small vessel ischemic changes. On Study Day 83, an MRI of the head without contrast showed a moderate burden of new scattered small acute infarcts throughout the bilateral cerebral and cerebellar hemispheres, the left caudate nucleus is involved, the supratentorial distribution is somewhat of a watershed distribution, correlating T2/FLAIR hyperintensities are present in these areas with no significant mass effect, no

⁸⁷ The dose of alteplase was confirmed in a response dated September 28, 2023 to an information request dated September 27, 2023.

hemorrhagic conversion is seen, and a remote lacunar infarct is present in the right basal ganglia. The impression of the MRI noted that given the moderate burden of scattered small acute infarcts throughout the bilateral cerebral and cerebellar hemispheres involving multiple vascular distributions, embolic disease should be considered. On Study Day 84, the subject's family opted for Do-Not-Resuscitate status. A chest x-ray obtained on Study Day 85 showed unchanged bilateral airspace disease. On the same day, the subject became hypoxic, bradycardic, and then died. The cause of death was reported as complications of Covid-19. An autopsy was not performed.

Reviewer comment: A role for donanemab in the SAE of Covid-19 pneumonia cannot be ruled out as pneumonia was among the most frequently reported SAEs in the placebo-controlled pool. A role for donanemab in the cerebral infarcts cannot be established because of the concurrent event of atrial fibrillation, which may have been a predisposing factor for the development of cerebral infarction, as a source of a potential embolism or as the source of a hypotensive event resulting in infarction.

One additional case related to the topic of cerebral infarction/cerebral ischemia, with death occurring outside of the 76-week on-study approach is noted (I5T-MC-AACI- (b) (6)). A role for donanemab could not be established in this case because of a lack of information (cerebrovascular accident, I5T-MC-AACI- (b) (6)). In this case, a 75 year-old female with history of coronary artery disease, carotid artery occlusion, ApoE ε3/ε3 status, hypertension, hyperlipidemia, atrial fibrillation, who was admitted to the hospital for carotid endarterectomy and experienced a cerebrovascular accident 20 days after the 17th dose and died approximately four months later. Whether an autopsy was performed is unknown.

Fatal Outcomes related to Pneumonia

Six SAEs with fatal outcome related to the topic of pneumonia were reported in the all-donanemab pool. Preferred terms for the five SAEs included pneumonia (n=2), acute respiratory failure, Covid-19, Covid-19 pneumonia, and aspiration pneumonia.

In the placebo-controlled pool, four donanemab-treated subjects experienced AEs with fatal outcome related to pneumonia compared to two on placebo (0.4% versus 0.2%, respectively).⁸⁸

This reviewer notes that all 6 cases in the all-donanemab pool had age (≥75 years) and dementia (based on MMSE score at baseline) as a risk factor for pneumonia. In four of the six cases, this reviewer notes that a role for donanemab could not be excluded given that pneumonia was among the SAEs with highest incidence in the donanemab arm and greatest

⁸⁸ Donanemab arm: I5T-MC-AACG- (b) (6) /pneumonia, I5T-MC-AACI- (b) (6) /Covid-19, and I5T-MC-AACI- (b) (6) /Covid-19 pneumonia; I5T-MC-AACI- (b) (6) /pneumonia; Placebo arm: I5T-MC-AACI- (b) (6) /respiratory failure and I5T-MC-AACI- (b) (6) /sepsis

difference from placebo in the placebo-controlled pool.⁸⁹ In the remaining two cases, this reviewer did not identify a role for donanemab in the SAE of aspiration pneumonia because of concurrent events of diarrhea, hypokalemia, atrial fibrillation, and cardiopulmonary resuscitation (I5T-MC-AACI- (b) (6)) or a case of pneumonia that occurred greater than 6 months after the last donanemab dose (I5T-MC-AACI- (b) (6)). The following table summarizes the six SAEs with fatal outcome related to the topic pneumonia.

Table 65. Fatal Outcome Related to the Topic of Pneumonia.

USUBJID Preferred Term Pool	Age/ Sex	AE onset Study Day	Notes
A role for donanemab in the SAE with fatal outcome could not be excluded given that pneumonia was among the SAEs with highest incidence in the donanemab arm and greatest difference from placebo in the placebo-controlled pool.			
I5T-MC-AACG- (b) (6) PT: Pneumonia PC	85 F	36	PMH of CAD s/p CABG, HTN, TIA, nephropathy, moderate dementia. Event onset: 4 days after the 2 nd dose.
I5T-MC-AACI- (b) (6) PT: Covid-19 pneumonia PC	82 M	70	PMH of chronic bronchitis, asthma, and COPD, DM2 with nephropathy, unvaccinated status for Covid-19 were likely contributory factors. Also with PMH of mild dementia. On Study Day 83, the subject become hypoxic, bradycardic, and then died. The cause of death was reported as complications of Covid-19. An autopsy was not performed. This subject is also discussed in the section on AEs with fatal outcome related to cerebral infarction as the subject was later diagnosed with multiple cerebral infarcts while hospitalized. Event onset: 15 days after the 3 rd dose

⁸⁹ I5T-MC-AACG- (b) (6) I5T-MC-AACI- (b) (6) I5T-MC-AACI- (b) (6) and I5T-MC-AACI- (b) (6)

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USUBJID Preferred Term Pool	Age/ Sex	AE onset Study Day	Notes
I5T-MC-AACI- (b) (6) PT: Covid-19 PC	79 M	346	The subject presented to the ER unresponsive and was found to have a UTI and Covid pneumonia. He had received two doses of Covid vaccine approximately a year before. Other potential contributory factors to the SAE of pneumonia included the subject's PMH of COPD. PMH of mild dementia Event onset: 9 days after the 13th dose.
I5T-MC-AACI- (b) (6) PT: Acute respiratory failure AP	75 F	38	The acute respiratory failure occurred in the setting of multifocal pneumonia and pneumonia was among the most frequently reported SAEs in the placebo-controlled pool. The subject's history of COPD was a likely contributory factor to the event of acute respiratory failure and pneumonia. PMH of mild dementia Event onset: 7 days after the 2nd dose
A role cannot be established.			
I5T-MC-AACI- (b) (6) PT: pneumonia PC	85 F	214	Event onset: 186 days after the 2nd dose.
I5T-MC-AACI- (b) (6) PT: Pneumonia aspiration AP	77 F	408	Concurrent events of atrial fibrillation, cardiopulmonary resuscitation, SAE of hypokalemia were likely contributory to the event of aspiration pneumonia. PMH of coronary artery disease, gastroesophageal reflux disease,

USUBJID Preferred Term Pool	Age/ Sex	AE onset Study Day	Notes
			hyperlipidemia, hypertension, Rheumatoid Arthritis, diabetes mellitus type 2, mild dementia. Event onset: 43 days after the 12 th dose

AF: Atrial fibrillation. AP: All-donanemab pool. CABG: Coronary artery bypass grafting. CAD: Coronary artery disease. COPD: Chronic obstructive pulmonary disease. DM2: diabetes mellitus type 2. DVT: deep vein thrombosis. GERD: gastroesophageal reflux disease. HL: hyperlipidemia. HTN: hypertension. PC: placebo-controlled pool. PMH: past medical history. TIA: transient ischemic attack. UTI: urinary tract infection.

Fatal Outcomes Related to the Topic of Dehydration

Two SAEs with fatal outcome with preferred term of dehydration were reported in the all-donanemab pool.

This reviewer identified one donanemab-treated subject who experienced the SAE of dehydration compared to none on placebo in the placebo-controlled pool, (0.1% versus none, respectively).⁹⁰

This reviewer did not identify a role for donanemab in one of the cases as the SAE occurred 121 days after the last dose of donanemab (I5T-MC-AACI- (b) (6)).

In the remaining case, from the placebo-controlled period of Study AACI, a role for donanemab could not be established given likely contributory factors. The case is summarized here.

Dehydration, I5T-MC-AACI- (b) (6)

This is a 68 year-old male with past medical history of mild dementia due to AD, visual hallucinations related to AD, hypertension, diabetes mellitus type 2, hypercholesterolemia, who developed the SAE of dehydration on Study Day 78 with fatal outcome. The subject had received the 2nd dose of donanemab 55 days prior to the event of dehydration. The subject experienced the AE of delirium on Study Day 38. On Study Day 42, he was noted to have a low sodium at 126 mmol/L (reference range not reported). On Study Day 43, he was hospitalized for the SAE of delirium and was noted have a low sodium of 119 mmol/L as well as urinary retention and a low grade fever. An MRI three days later showed mild chronic microvascular ischemic changes. On Study Day 50, he developed dysphagia. On Study Day 78, the SAE of dehydration was reported and he passed on Study Day 81 due to the SAE of dehydration. The

⁹⁰ Donanemab arm: I5T-MC-AACI- (b) (6)

subject's family was reported to have opted for palliative care. The death certificate noted the leading cause of death was dehydration due to dysphagia and dementia. Concomitant medications at the start of the study included acetylsalicylic acid, glargine; lixisenatide, indapamide; perindopril, metformin, propranolol, and rosuvastatin.

The following table outlines the course of events in further detail.

Table 66. Narrative for IST-MC-AACI- (b) (6) with Fatal Outcome of Dehydration.

Study Day	Events
38	The subject was reported to experience the AE of delirium (verbatim term: paranoid delirium with psychotic elements) characterized by wandering, loss of appetite, and restlessness. The subject was prescribed risperidone and an MRI was ordered.
40	The subject experienced more visual hallucinations and was threatening to harm himself and others and was seen in the ER.
42	AE of hyponatremia (moderate) and was noted to have a low sodium of 126 mmol/L. He was started on trazodone and was reported to have correction of the hyponatremia at the hospital the same day.
43	The subject was hospitalized for the SAE of delirium (verbatim term: paranoid delirium with psychotic elements). On that day, the subject was also reported to have a low grade fever, urinary retention, hematuria, and a fall. The sodium was 119 mmol/L. A CT of the head on that day was normal and a chest x-ray was normal. He was reported to have been treated with trazodone.
46	The subject had an MRI that showed mild chronic microvascular ischemic changes. There was no evidence of acute infarction, no space-occupying lesion or mass-effect, no extra-axial collection, intracranial hemorrhage or focal mass lesion, and no evidence of cortical infarction or intracranial hemorrhage.
47	Sodium was 128 mmol/L
48	AE of urinary retention (mild) was reported
49	For symptom management of the behavior concerns, the subject was prescribed quetiapine 12.5 mg prn, loxapine prn, and trazodone daily and prn.
50	AE of dysphagia (severe) was reported. The sodium was at 135 mmol/L and the subject was considered to have recovered from hyponatremia.
55	A urine analysis showed 2 + leukocytes, 3+ blood, and 2 + protein.
78	The subject's hospitalization was prolonged because of the SAE of dehydration.
81	The subject died due to the SAE of dehydration. The death certificate noted the leading cause of death was dehydration due to dysphagia and dementia. An autopsy was not performed. The family was reported to have opted for palliation due to the conditions of dysphagia and dementia.

Reviewer comment: A role for donanemab in the fatal event of dehydration cannot be established given the preceding AE of dysphagia as well as likely contributory factor of being placed on palliative care. . A role for donanemab in the AE of dysphagia is possible as TEAEs of dysphagia were reported with higher incidence in the donanemab arm compared to placebo in the placebo-controlled pool (0.7% [7/984] versus 0.4% [4/999]). This reviewer notes that the AE of delirium in the case was most likely secondary to hyponatremia, given co-occurrence of the events.

Fatal Outcomes Related to the Topic of Pulmonary Embolism

Two SAEs of pulmonary embolism with fatal outcome were reported. In one case, a role for donanemab could not be ruled out as pulmonary embolism was among the SAEs reported with highest incidence and greatest difference from placebo in the placebo-controlled pool.

Pulmonary embolism, IST-MC-AACI- (b) (6)

The case involved a 69 year-old female with past medical history of hypertension, hyperlipidemia, diabetes mellitus type 2, hereditary spherocytosis, mitral valve prolapse, atrial fibrillation, and sleep apnea who developed the SAE of pulmonary embolism 2 days after the first dose on Study Day 3. Her labs approximately one month before were notable for an elevated proBNP of 816 (reference range not provided) and a decreased estimated glomerular filtration rate of 55 (reference range not provided). She did not report any symptoms after the first dose of study drug. Two days after the first dose, she was found deceased in her bed. An autopsy showed a pulmonary embolism in the left main and lobar arteries in the left lung. The subject also had right ventricular dilatation, hepatomegaly, and splenomegaly. Multiple granulomata were identified in her lungs and hilar lymph nodes that were negative for acid-fast bacillus that were suggestive of sarcoidosis. The final autopsy report indicated venous thromboembolism associated with the subject was likely to be provoked by risk factors including immobilization due to Alzheimer's disease. Neuropathological changes were reported to be consistent with an intermediate level of AD. Cerebrovascular disease included moderate to severe cerebral amyloid angiopathy, moderate hypertensive cerebrovascular disease, and moderate atherosclerosis of the cerebral vessels. Concomitant medications included apixaban (5 mg daily), atorvastatin, calcium carbonate, vitamin D3, cyanocobalamin, digoxin, donepezil, famotidine, fexofenadine, fluticasone, folic acid, glyburide, hydrochlorothiazide, ferrous sulfate, liraglutide, lisinopril, metformin, acetaminophen, rivastigmine, albuterol, and sertraline.

Reviewer comment: The case reports death in a subject who was found on autopsy to have pulmonary embolism. A role for donanemab in the event of pulmonary embolism cannot be ruled out as pulmonary embolism was among the among one the SAEs reported with highest

incidence and greatest difference from placebo *in the placebo-controlled pool. The subject's past medical history of atrial fibrillation, hypertension, and sleep apnea are potential contributory factors to the development of pulmonary embolism.*

In the second case of pulmonary embolism with fatal outcome, this reviewer did not identify a role for donanemab given confounding with concomitant medication use with raloxifene, which carries a boxed warning for pulmonary embolism (I5T-MC-AACI- (b) (6)).

Fatal Outcomes Related to Respiratory Failure

This reviewer noted three cases related to respiratory failure (preferred terms: respiratory failure [n=2] and respiratory arrest).

In the placebo-controlled pool, two donanemab-treated subject experienced an AE with fatal outcome related to respiratory failure compared to one on placebo (0.2% versus 0.1%, respectively).⁹¹

One case of respiratory failure with fatal outcome occurred in the setting of hospitalization for worsening carotid artery disease requiring stent placement (I5T-MC-AACI- (b) (6)). In this case, an 84-year old subject with past medical history of coronary artery disease, congestive heart failure, atrial fibrillation, aortic valve replacement, and pulmonary hypertension was found to not be breathing overnight during a nursing check. Cardiopulmonary resuscitation was administered; however, the subject was unable to be revived. An autopsy was not performed and the death certificate was unavailable. The last dose of donanemab had been 24 days prior to the event of respiratory failure (10th dose). Given the lack of information in this case for cause of respiratory failure, this reviewer did not establish a role for donanemab in the event.

In the second case, this reviewer did not identify a role for donanemab because of concurrent events that were likely contributory to the fatal outcome including gastric outlet obstruction, pancreatitis, and ureteropelvic junction obstruction (I5T-MC-AACI- (b) (6)).

In the third case, this reviewer did not identify a role for donanemab as the most recent dose of donanemab had been greater than 6 months prior to the fatal outcome (I5T-MC-AACI- (b) (6)).

The following table summarizes the cases related to respiratory failure.

⁹¹ Donanemab arm: I5T-MC-AACI- (b) (6) Placebo arm: I5T-MC-AACI- (b) (6).

Table 67. Fatal Outcome with Preferred Terms of Respiratory Failure or Respiratory Arrest.

USUBJID Preferred Term Pool	Age/ Sex	AE onset Study Day	Notes
I5T-MC-AACI- (b) (6) PT: Respiratory failure AP	84 M	282	PMH of coronary artery disease, s/p coronary artery bypass graft, congestive heart failure, atrial fibrillation, aortic valve replacement, gastroesophageal reflux disease, hypertension, hyperlipidemia, pulmonary hypertension Concurrent event of hospitalization for stent placement for carotid artery disease 24 days after the 10 th dose
I5T-MC-AACI- (b) (6) PT: respiratory failure PC	77 F	514	PMH of hypertension, hyperlipidemia, chronic kidney disease, supraventricular arrhythmia, Covid-19 on SD 273, hospitalized for pneumonia on SD 356 (resolved SD 366), and discontinued from the study on SD 386 for pneumonia. On SD 514, the subject died of severe respiratory failure while hospitalized. The primary cause of death on the death certificate was unspecified dementia. No autopsy was performed. Further information related to details of hospitalization was not available. 184 days after the 13 th dose
I5T-MC-AACI- (b) (6) PT: Respiratory Arrest PC	72 M	331	Concurrent events of gastric outlet obstruction suspected to be secondary to metastatic disease, pancreatitis, and severe right hydronephrosis secondary to right ureteropelvic junction obstruction were likely contributory factors

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USUBJID Preferred Term Pool	Age/ Sex	AE onset Study Day	Notes
			50 days after the 11 th dose

AP: All-donanemab pool. PC: Placebo-controlled pool.

Suicide

Two SAEs with fatal outcome with preferred term of completed suicide were reported in the all-donanemab pool.

Both cases occurred in the placebo-controlled period of AACI. In the placebo-controlled pool, a similar incidence of AEs with fatal outcome related to suicide occurred in the donanemab and placebo arms (0.2% versus 0.1%, respectively).⁹²

This reviewer did not establish a role for donanemab in either case of suicide in donanemab-treated subjects because of past medical history, which may have been a predisposing factor. The following table summarizes the two cases related to suicide.

Table 68. Fatal Outcome Related to Suicide

USUBJID Preferred term Pool	Age/ Sex	AE onset Study Day	Notes
I5T-MC-AACI- (b) (6) PT: Completed suicide PC	63 M	174	PMH of one episode of paranoia/delusion, circadian sleep disorder, hypothyroidism, obstructive sleep apnea, and. In the two weeks preceding the event, he was noted to be more paranoid, anxious, confused, and had worsening vision and delusional behavior. Event onset: 35 days after the 6 th dose.
I5T-MC-AACI- (b) (6) PT: Completed Suicide PC	75 M	314	PMH of depression Event onset: 5 days after the 12 th dose.

AP: All-donanemab pool. PC: Placebo-controlled pool. PMH: past medical history

⁹² Donanemab arm: I5T-MC-AACI- (b) (6) and I5T-MC-AACI- (b) (6) Placebo arm: I5T-MC-AACI- (b) (6)

Fatal Outcomes Related to Falls or Trauma

Two AEs with fatal outcome related to the topic of trauma were reported, both from the all-donanemab pool. Preferred terms included Gunshot wound and Head injury.

Additionally, this reviewer notes a case from the placebo-controlled pool with SAE of subarachnoid hemorrhage with fatal outcome that occurred after a fall and is discussed above in the Intracerebral Hemorrhage section above (subarachnoid hemorrhage, [I5T-MC-AACI-](#) (b) (6)).

In addition to the above cases, one additional fatal case related to fall (preferred term of death) occurred 4 days after the end of the placebo-controlled period of AACI (on Study Day 536, I5T-MC-AACI- (b) (6)).

Three of the four fatal cases involved a fall, and a role for donanemab could not be ruled out as falls were among the most frequently reported SAEs in the placebo-controlled pool (head injury, I5T-MC-AACI- (b) (6) death, I5T-MC-AACI- (b) (6) and subarachnoid hemorrhage, I5T-MC-AACI- (b) (6)). In the subject who experienced an SAE of subarachnoid hemorrhage after a fall, other likely contributory factors for falling included the subject's history of unsteadiness and falls, and concurrent use of a ladder ([I5T-MC-AACI-](#) (b) (6)).

In the fourth case, this reviewer did not identify a role for donanemab because of concurrent events (gunshot wound, I5T-MC-AACI- (b) (6)).

The following table summarizes the three cases with fatal outcome related to the topic of trauma with preferred term of gunshot wound, head injury, or death.

Table 69. Fatal Outcome of Cases Related to the Topic of Trauma with Preferred Term of Gunshot Wound, Head Injury, or Death.

USUBJID Preferred Term Pool	Age/ Sex	AE onset Study Day	Notes
I5T-MC-AACI- (b) (6) PT: Gunshot wound AP	83 M	41	Concurrent events: As per the death certificate, the subject was shot by another person with a shotgun. Most recent post-baseline MRI: none 12 days after 2 nd dose
I5T-MC-AACI- (b) (6)	86 M	335	Concurrent event of fall. The subject

USUBJID Preferred Term Pool	Age/ Sex	AE onset Study Day	Notes
PT: Head injury AP			sustained a head injury after a fall in a parking lot. ⁹³ The cause of death was listed as due to complications from blunt force injury to the head. An autopsy was not performed. Most recent post-baseline MRI: Study Day 172: Superficial siderosis measuring 13 mm (12 mm at baseline). 23 days after the 12 th dose
I5T-MC-AACI- (b) (6) PT: Death PC ^a	81 F	536	Concurrent events: multiple fractures from an unwitnessed fall in an apartment in an assisted living facility. ⁹⁴ Most recent post-baseline MRI: Study Day 356: focal white matter lesions 37 days after the 19 th dose

AP: All-donanemab pool. PC: Placebo-controlled pool

^aThe fatal event occurred 4 days after the 76-week placebo-controlled period of AACI.

In the remaining 10 cases, this reviewer notes one case of renal failure in the all-donanemab pool where a role for donanemab could not be ruled out. The case is summarized here.

Renal failure, I5T-MC-AACI- (b) (6)

65 year-old female with past medical history of hypertension, hyperlipidemia, migraine, anxiety, visual hallucinations who was hospitalized for the SAEs of renal failure (moderate) and urinary tract infection (moderate) on Study Day 689, 32 days after the second dose of donanemab. The subject was unable to urinate that day. She had been experiencing dysuria for three weeks, hallucinations for five days, and vomiting for two days, and loss of appetite. Vital signs four days prior to hospitalization (Study Day 685) showed a blood pressure of 126/80 mmHg, pulse rate of 59 beats per minute, and temperature of 37 degrees Celsius. On Study Day 685, the subject experienced the AE of confusion and did not receive the study drug. On the day of hospitalization, the creatinine was 5.7 mg/dL (reference range of 0.52 – 1.04), and the

⁹³ Noted in the Applicant's response dated August 28, 2023, to an information request dated August 25, 2023.

⁹⁴ Noted in the Applicant's response dated August 28, 2023, to an information request dated August 25, 2023.

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kidney failure was considered to be acute. She was treated with ceftriaxone and given intravenous fluids. The kidney function worsened over the next several days and the subject was started on dialysis. The subject's family requested a hospice evaluation. On Study Day 701, the subject was discharged from the hospital to hospice. The following day, the subject died due to the event of renal failure. It was not known if an autopsy was done. The cause of kidney failure was reported to be due to encephalopathy, urinary tract infection, and dehydration. Eighteen days prior to the SAEs of renal failure and UTI, the subject had experienced the adverse event of agitation (moderate). Concomitant medications included escitalopram, famotidine, fluticasone, hydrocodone for myoclonus, levetiracetam for myoclonus, metoprolol, omega-3 fatty acids, ramipril, rizatriptan prn, and quetiapine.

Reviewer comment: This reviewer could not rule out a role for donanemab in the event of renal failure given onset with donanemab dosing. Likely contributory factors to the SAE of renal failure was the SAE of UTI. Risk factors for the SAE of UTI include female sex.

The following table contains this reviewer's summary of information in the remaining 9 cases with AEs with fatal outcomes in the all-donanemab pool. In these cases, a role for donanemab could not be established because of additional contributory factors, such as presence of medical history, concomitant medications, or concurrent events (n=4), or because of a lack of information (n=2), or because the time from the last dose of donanemab to onset of the AE was greater than 57 days (n=2).

Table 70. Summary of Remaining 8 Cases of AEs with Fatal Outcome in Donanemab-Treated Subjects.

USUBJID Preferred Term Pool	Age/ Sex	AE onset Study Day	Notes
A role cannot be established due to concurrent events, concomitant medication use, or PMH.			
I5T-MC-AACI- (b) (6) PT: Dementia Alzheimer's type PC	84 F	154	1 month post SAE of acute myocardial infarction on Study Day 103. Developed severe esophagitis with gastric erosions. Refused to take medications and sent to hospice PMH: gastroesophageal reflux disease, hypertension, hyperlipidemia 56 days after the 3rd dose
I5T-MC-AACI- (b) (6) PT: pancreatic carcinoma	79 M	427	Risk factors for pancreatic cancer included history of tobacco use and

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USUBJID Preferred Term Pool	Age/ Sex	AE onset Study Day	Notes
metastatic AP			diabetes mellitus 55 days after the 14 th dose
I5T-MC-AACI- (b) (6) PT: Retroperitoneal hemorrhage PC	82 F	267	On warfarin for PMH of AF. Presented with abdominal pain and was diagnosed with retroperitoneal hemorrhage. Renal failure worsened, also with thrombocytopenia. The subject did not have a titration period of 700 mg for the first three doses. SAE occurred 12 days after the 10 th dose.
A role cannot be established due to lack of information.			
I5T-MC-AACI- (b) (6) PT: Death PC	83 F	63	Information lacking – the investigation site had not received a death certificate and an autopsy was not performed. The subject died in her sleep. PMH of HTN, HL, previous infarct on screening MRI. ⁹⁵ Concomitant meds include alprazolam. 35 days after the 2 nd dose.
I5T-MC-AACI- (b) (6) PT: Death AP	80 M	204	Lack of information on the cause of death. An autopsy was not performed. PMH of Attention deficit hyperactivity disorder, chronic obstructive pulmonary disease, coronary artery disease, diabetes mellitus type 2, Chronic lymphocytic leukemia. 31 days after the 7 th dose
A role cannot be established due to onset of AE and time from the last dose of donanemab			
I5T-MC-AACG- (b) (6) a PT: Metabolic encephalopathy	77 M	545 – 550	AE onset > 125 days after the most recent dose.

⁹⁵ Noted in the Applicant's response dated August 28, 2023, to an information request dated August 25, 2023.

USUBJID Preferred Term Pool	Age/ Sex	AE onset Study Day	Notes
AP			
I5T-MC-AACG- (b) (6) PT: Cardiac failure congestive AP	76 M	438	AE onset 209 days after the 9 th dose PMH: cardiomyopathy, chronic left ventricular failure, hyperlipidemia, diabetes mellitus type 2, ventricular extrasystoles
I5T-MC-AACI- (b) (6) b PT: Aortic dissection AP	84 M	660	AE onset 180 days after the most recent dose of donanemab; on placebo in the long term extension of AACI
I5T-MC-AACI- (b) (6) PT: Dementia with Lewy Body disease AP	70 F	329	AE onset 156 days after the most recent donanemab dose
I5T-MC-AACI- (b) (6) PT: cardiac arrest AP	75 F	424	AE onset 180 days after the most recent donanemab dose
I5T-MC-AACI- (b) (6) PT: pelvic fracture AP	81 M	287	AE onset 116 days after the most recent donanemab dose
I5T-MC-AACI- (b) (6) PT: myocardial infarction AP	75 F	323	AE onset 210 days after the most recent donanemab dose

AP: All-donanemab pool. PC: Placebo-controlled pool. PMH: past medical history.

^aThe subject's AE with fatal outcome exact start date was unknown.

^bThe last dose of placebo had been within 57 days of the AE with fatal outcome.

One subject from Study AACG was noted to have a fatal outcome > 200 days after the end of the study (preferred term of death, I5T-MC-AACG- (b) (6)). This reviewer did not identify a role for donanemab in this case given the length of time between the last dose of donanemab and the onset of the adverse event.

13.8. SAEs by Preferred Term in the Placebo-Controlled Period of AACI and the Placebo-controlled Pool

The following table shows SAEs with incidence of at least 0.2% higher in the donanemab arm compared to placebo in the placebo-controlled period of AACI.

Table 71. SAEs with Incidence of at Least 0.2% Higher in the Donanemab Arm Compared to Placebo in the Placebo-controlled Period of AACI

Preferred Terms	Donanemab (N = 853)	Placebo (N = 874)
Total Subjects with any Adverse Events	140 (16.4%)	124 (14.2%)
Amyloid related imaging abnormality-edema/effusion	13 (1.5%)	0 (0.0%)
Acute myocardial infarction	4 (0.5%)	0 (0.0%)
Amyloid related imaging abnormality-microhemorrhages and hemosiderin deposits	4 (0.5%)	0 (0.0%)
COVID-19	7 (0.8%)	4 (0.5%)
Agitation	4 (0.5%)	1 (0.1%)
Fall	4 (0.5%)	1 (0.1%)
Death	2 (0.2%)	0 (0.0%)
Dehydration	3 (0.4%)	0 (0.0%)
Intestinal obstruction ^a	3 (0.4%)	0 (0.0%)
Subdural hematoma	3 (0.4%)	0 (0.0%)
Pneumonia	5 (0.6%)	3 (0.3%)
Acute kidney injury	4 (0.5%)	2 (0.2%)
Seizure	3 (0.4%)	1 (0.1%)
Benign prostatic hyperplasia	2 (0.2%)	0 (0.0%)
Non-cardiac chest pain	2 (0.2%)	0 (0.0%)
Pancreatitis acute	2 (0.2%)	0 (0.0%)
Plasma cell myeloma	2 (0.2%)	0 (0.0%)
Pneumothorax	2 (0.2%)	0 (0.0%)

This table was created by Senior Clinical Analyst Dr. Rui Li using the 90-Day Safety ADAE dataset.

^aGrouped term of intestinal obstruction includes the preferred term of small intestinal obstruction and excludes IST-MC-AACI- (b) (6) who reported small intestinal obstruction more than 6 months from the last dose of donanemab.

The following table shows SAEs by preferred term with incidence of at least 0.2% higher in the donanemab arm compared to placebo in the placebo-controlled pool.

Table 72. SAEs by Preferred Term with Incidence of at Least 0.2% Higher in the Donanemab Arm Compared to Placebo in the Placebo-controlled Pool

Preferred Term	Donanemab N=984 n (%)	Placebo N=999 n (%)
Total Subjects with any SAEs	162 (16.5)	143 (14.3)
Amyloid related imaging abnormality-edema/effusion	15 (1.5)	0
Pneumonia	10 (1)	3 (0.3)
Acute myocardial infarction	4 (0.4)	0
Amyloid related imaging abnormality-microhemorrhages and hemosiderin deposits	4 (0.4)	0
Dehydration	5 (0.5)	1 (0.1)
Intestinal obstruction ^a	4 (0.4)	0
Subdural hematoma	4 (0.4)	0
Fall	4 (0.4)	1 (0.1)
Death	2 (0.2)	0
Infusion related reaction	3 (0.3)	0
Pulmonary embolism	5 (0.5)	2 (0.2)
Covid-19	7 (0.7)	4 (0.4)
Acute kidney injury	4 (0.4)	2 (0.2)
Agitation	4 (0.4)	2 (0.2)
Benign prostatic hyperplasia	2 (0.2)	0
Pancreatitis acute	2 (0.2)	0
Plasma cell myeloma	2 (0.2)	0
Pneumothorax	2 (0.2)	0
Sinus node dysfunction	2 (0.2)	0
Seizure	3 (0.3)	1 (0.1)

This reviewer created this table using the 90-Day Safety IDB ADAE dataset, AESER = Y, TEPCLDLFL, APERIODC= First treatment period.

^aGrouped term of intestinal instruction includes the preferred term of small intestinal obstruction and excludes I5T-MC-AACI- (b) (6) who reported small intestinal obstruction more than 6 months from the last dose of donanemab.

13.9. EMQ and FMQ Groupings for SAEs in the All-Donanemab Pool

The following table shows SAEs by grouped terms with incidence of at least 1% in the all-donanemab pool after the 90-Day Safety Update.

Table 73. SAEs by Grouped Terms with Incidence of at Least 1% in the All-Donanemab Pool after the 90-Day Safety Update

Grouped Terms	Donanemab N=2802 n (%)
Infection	59 (2.1)
Pneumonia	18 (0.6)
Urinary tract infection	9 (0.3)
Diverticulitis	5 (0.2)
Sepsis	5 (0.2)
Cellulitis	3 (0.1)
Pneumonia aspiration	2 (0.1)
Appendicitis	1 (<0.5)
Appendicitis perforated	1 (<0.5)
Arthritis bacterial	1 (<0.5)
Bacterial sepsis	1 (<0.5)
Cholecystitis	1 (<0.5)
Cholecystitis acute	1 (<0.5)
Clostridium difficile colitis	1 (<0.5)
Cystitis	1 (<0.5)
Gastroenteritis	1 (<0.5)
Gastrointestinal infection	1 (<0.5)
Influenza	1 (<0.5)
Kidney infection	1 (<0.5)
Localized infection	1 (<0.5)
Peritoneal abscess	1 (<0.5)
Peritonitis	1 (<0.5)
Pneumonia legionella	1 (<0.5)
Salmonellosis	1 (<0.5)
Urinary tract infection pseudomonal	1 (<0.5)
Urosepsis	1 (<0.5)
Wound infection	1 (<0.5)
Fracture	37 (1.3)
Rib fracture	6 (0.2)
Hip fracture	5 (0.2)
Pelvic fracture	5 (0.2)
Humerus fracture	4 (0.1)
Femur fracture	3 (0.1)
Femoral neck fracture	2 (0.1)

Grouped Terms	Donanemab N=2802 n (%)
Lumbar vertebral fracture	2 (0.1)
Fracture displacement	1 (<0.5)
Multiple fractures	1 (<0.5)
Patella fracture	1 (<0.5)
Radius fracture	1 (<0.5)
Spinal compression fracture	1 (<0.5)
Spinal fracture	1 (<0.5)
Sternal fracture	1 (<0.5)
Thoracic vertebral fracture	1 (<0.5)
Ulna fracture	1 (<0.5)
Upper limb fracture	1 (<0.5)
Wrist fracture	1 (<0.5)

This reviewer created this table using the 90Day Safety IDB ADAE dataset, TELYLDFL, AESER = Y.

13.10. Narratives for Serious Adverse Events

This reviewer reviewed serious adverse events occurring on drug and up to 57 days after the last dose (~5-times the half-life of donanemab) as well as serious adverse events occurring with the Applicant's prespecified analysis of within the treatment period plus 57 days.⁹⁶

The review of narratives of SAEs related to topics of special interest included ARIA, intracranial hemorrhage, and hypersensitivity and infusion related reactions.

This reviewer also reviewed SAEs of other events of interest including SAEs related to cerebral infarction/cerebrovascular accident/ischemic stroke.

This reviewer reviewed the following events because of imbalances of SAEs were noted in the donanemab arm in the placebo-controlled pool: acute myocardial infarction, intestinal obstruction and perforation, colitis, gastroenteritis, gastritis/duodenitis, dehydration, hernia, pneumonia, pulmonary embolism, pancreatitis, fall, acute kidney injury, seizure, Covid-19, and non-cardiac chest pain.

This reviewer reviewed the following events because of a higher incidence of TEAEs was noted in the donanemab arm compared to placebo in the placebo-controlled pool: hyponatremic events and hyperglycemic events.

⁹⁶ SAEs occurring after the last dose + 57 days were identified in the ADAE dataset using TELY57FL=Y.

This reviewer also reviewed SAEs related to cardiac arrest, sinus node dysfunction, hypertension-related events, and suicide-related events.

ARIA-E

For the topic of ARIA-E, this reviewer searched the all-donanemab pool for SAEs with preferred terms of amyloid related imaging abnormality-edema/effusion, brain edema, and vasogenic cerebral edema.

This reviewer identified 34 SAEs of ARIA-E occurring in 34 subjects during the treatment period or up to 57 days after in the all-donanemab pool.⁹⁷ Preferred terms included amyloid related imaging abnormality-edema/effusion (n=32) and brain edema (n=2). A role for donanemab in the cases is likely given the time between AE onset and dosing of donanemab, and because ARIA has been associated with other approved amyloid-directed monoclonal antibody drugs.^{98,99}

Eighteen of the 34 subjects were female (52.9%). Median age was 74.5 years (range 64 to 84 years). Median number of donanemab doses received prior to developing the AE was 3. Screening MRIs showed microhemorrhage in 17.6% (6/34), superficial siderosis in 14.7% (5/34), and white matter disease in 94% (32/34) of the subjects. Of those with known ApoE ϵ 4 carrier status, 78.8% had at least one ApoE ϵ 4 allele (26/33).

Three of the 34 (8.8%) cases were fatal ([15T-MC-AACI-](#)(b) (6) [15T-MC-AACI-](#)(b) (6) and [15T-MC-AACI-](#)(b) (6)). This did not include an additional subject who received thrombolytic therapy and developed intracerebral hemorrhage in the setting of serious ARIA-E ([15T-MC-AACI-](#)(b) (6)).

The median duration of cases was 27 days (range 3 to 306).¹⁰⁰ Steroids were used to treat serious ARIA-E in 64.7% subjects (22/34). Serious ARIA-E was symptomatic in 88.2% of the cases

97 15T-MC-AACG- (b) (6) 15T-MC-AACG- (b) (6) 15T-MC-AACG- (b) (6) 15T-MC-AACG- (b) (6) 15T-MC-AACG- (b) (6)
MC-AACG- (b) (6) 15T-MC-AAACI- (b) (6) 15T-MC-AAACI- (b) (6) 15T-MC-AAACI- (b) (6) 15T-MC-AAACI- (b) (6) 15T-MC-AAACI- (b) (6)
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MC-AAACI- (b) (6) 15T-MC-AAACI- (b) (6) 15T-MC-AAACI- (b) (6) 15T-MC-AAACI- (b) (6) 15T-MC-AAACI- (b) (6) 15T-MC-AAACI- (b) (6)
(b) (6) 15T-MC-AAACI- (b) (6), 15T-MC-AAACI- (b) (6) and 15T-MC-AACN- (b) (6)

⁹⁸ Aduhelm. Labeling-Prescribing Information. Drugs@fda.gov. Action date February 8, 2023. Accessed August 25, 2023.

⁹⁹ Legembi. Labeling-Prescribing Information. Drugs@fda.gov. Action date July 6, 2023. Accessed August 24, 2023.

¹⁰⁰ Based on cases that had an end date recorded in the dataset. This included cases with the following outcomes: fatal, recovered/resolved, or recovered/resolved with sequelae status.

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(30/34). Confusional state was the symptom with highest incidence reported within 30 days of ARIA-E onset (7/34 [20.6%]).

Table 74. SAEs of ARIA-E in All-Donanemab Pool after the 90-Day Safety Update

Parameter	(N=34)
Sex	Male (16) Female (18)
Age (years)	Median: 74.5 Range: 64 – 84
Race	White (34)
e4 carrier status	Homozygous (12) Heterozygous (14) Non-carrier (7) Missing (1)
Screening MRI findings	Microhemorrhages: (6/34) Superficial siderosis (5/34) Lacunar Infarct (1/34) White Matter Disease: Focal Lesions (27/34) White Matter Disease: Beginning Confluence of Lesions (5/34)
Time Between SAE Onset and First Donanemab Infusion (Days)	Median: 68.5 days, Range: 16 – 426
Number of donanemab infusions prior to onset of ARIA-E	Median: 3.0, Range: 1 – 10
AE outcome	Recovered/Resolved (22) Fatal (3) ^a Not Recovered/Not resolved (3) ^b Recovering/Resolving (3) Recovered/Resolved with Sequelae (2)
Duration of AEs with Fatal, Recovered/Resolved or Recovered/Resolved with Sequelae status (days) ^c	n=27 Median: 36.0, Range: 3 – 306
Duration of AEs with	n=3

Parameter	(N=34)
Fatal status (days)	Median: 20, Range 14 – 36
Study Drug Disposition ^d	Drug withdrawn (21) Drug interrupted (6) Dose not changed (5) Not applicable (1) Unknown (1)
Treatment with steroids	Yes (22)
Symptomatic	Yes (30)
Symptoms reported to be associated with ARIA-E within 30 Days of onset of Serious ARIA-E	n=26 • Confusional State (n=7) • Headache (n=6) • Gait Disturbance, Mental Status Change, and Seizure (n= 4 for each) • Aphasia, dizziness, fatigue, and nausea (n=3 for each) • Altered state of consciousness, Cognitive disorder, Delirium, Disturbance in attention, Hypertension, Tremor, and Vomiting (n=2 for each) • Abnormal behavior, Acute respiratory failure, Asthenia, Ataxia, Balance disorder, Blindness, Bradycardia, Cerebral microhemorrhage, Coordination abnormal, Diplopia, Encephalopathy, Hemiparesis, Hemiplegia, Hypokalemia, Hypomagnesemia, Hypotension, Illusion, Imperception, Incontinence, Movement disorder, Psychomotor retardation, Speech disorder, Vision blurred, and Visual impairment (one each)

^aThis includes I5T-MC-AACI- (b) (6) I5T-MC-AACI- (b) (6) and I5T-MC-AACI- (b) (6)

^bThis includes I5T-MC-AACI- (b) (6) whose outcome in the adverse event dataset was listed as unknown.

^cThis does not include I5T-MC-AACI- (b) (6) where the outcome was listed as recovered/resolved; however, did not have a date for resolution of the event.

^dTreatment Status noted as not applicable in I5T-MC-AACI- (b) (6) who had intracerebral hemorrhage, and fatal outcome in the setting of thrombolytic administration. Treatment status for I5T-MC-AACG- (b) (6) was noted as not applicable in the dataset and was noted to have been discontinued because of the adverse event in a review of the narrative.

ARIA-H

For the topic of ARIA-H, this reviewer searched the all-donanemab pool for SAEs with preferred term of amyloid related imaging abnormality-microhemorrhages and hemosiderin deposits and superficial siderosis of the central nervous system.

This reviewer identified nine SAEs of ARIA-H, all microhemorrhage, occurring in nine subjects in

the all-donanemab pool using the treatment period plus 57 days method.¹⁰¹ All of the cases had the preferred term amyloid related imaging abnormality-microhemorrhages and hemosiderin deposits. A role for donanemab in the cases is likely given the time between AE onset and dosing of donanemab, and because ARIA-H microhemorrhage has been associated with other approved amyloid-directed monoclonal antibody drugs.^{102,103}

In two of the nine cases, the subject had concomitant thrombotic use (I5T-MC-AACI- (b) (6) aspirin 81 mg daily and I5T-MC-AACI- (b) (6), clopidogrel 75 mg daily).

Six of the nine cases had concurrent serious ARIA-E.

Screening MRIs were normal in 2 of the 9 subjects (22.2%). Two (22.2%) had microhemorrhage, four (44.4%) had superficial siderosis, and seven (77.8%) had white matter disease on screening MRI.

Two of the nine cases are discussed in the Deaths section of this review (I5T-MC-AACI- (b) (6) (b) (6) [a case that also reported ARIA-E with fatal outcome](#), and I5T-MC-AACI- (b) (6) (b) (6) a case that also reported intracerebral hemorrhage).

Of the remaining seven cases, five cases reported SAEs of ARIA-E and are included in the review of narratives of SAEs of ARIA-E above.¹⁰⁴ In the sixth case, the subject also experienced the SAE of cerebral infarction and is discussed later in this section (I5T-MC-AACI- (b) (6)).

In the remaining case, an 83 year-old female homozygous for ε3 developed slurred speech and difficulty speaking, five days after the fourth dose of donanemab and was hospitalized and was found to have ARIA-H microhemorrhage of moderate severity on Study Day 154 (I5T-MC-AACI- (b) (6)). She received labetalol and physical therapy and was discharged from the hospital four days later and had not recovered from the event at the time of the data cutoff. Twenty-nine days later, the drug was permanently discontinued. An MRI 32 days later showed superficial siderosis of 40 mm in the right frontal lobe, an infarct in the left frontal lobe, and a lacunar infarct in the right frontal lobe that were new. The baseline MRI showed lacunar infarcts in the left frontal lobe and bilateral deep grey matter structures. The subject was not on antithrombotic therapy.

Intracranial Hemorrhage

¹⁰¹ I5T-MC-AACG- (b) (6) I5T-MC-AACG- (b) (6) I5T-MC-AACI- (b) (6) I5T-MC-AACI- (b) (6) I5T-MC-AACI- (b) (6) I5T-MC-AACI- (b) (6) I5T-MC-AACI- (b) (6), and I5T-MC-AACI- (b) (6).

¹⁰² Aduhelm. Labeling-Prescribing Information. Drugs@fda.gov. Action date February 8, 2023. Accessed August 25, 2023.

¹⁰³ Leqembi. Labeling-Prescribing Information. Drugs@fda.gov. Action date July 6, 2023. Accessed August 24, 2023.

¹⁰⁴ I5T-MC-AACG- (b) (6) I5T-MC-AACG- (b) (6) I5T-MC-AACI- (b) (6) I5T-MC-AACI- (b) (6) and I5T-MC-AACI- (b) (6).

For the topic of intracranial hemorrhage, this reviewer searched the all-donanemab pool for SAEs with preferred terms belonging to the EMQ/FMQ Grouping of Intracranial Hemorrhage (the reader is referred to the [Appendix](#) for preferred terms within this grouping).

In the all-donanemab pool, this reviewer identified 16 SAEs, occurring in 13 subjects, related to the topic of intracranial hemorrhage that occurred while on drug or within 57 days from the last dose. The following preferred terms were reported in the 15 SAEs: Subdural hematoma (n=5); Subarachnoid hemorrhage (n = 4); Hemorrhagic stroke (n=3); and Cerebral hemorrhage, Extradural hematoma, Hemorrhage intracranial, and Thalamus Hemorrhage (n=1 for each).

Three of the SAEs related to the topic of intracranial hemorrhage had fatal outcome and are discussed in the Deaths section of this review (thalamus hemorrhage, intracerebral hemorrhage, and subarachnoid hemorrhage). In the case of thalamic hemorrhage, the subject had past medical history of hypertension as a risk factor ([I5T-MC-AACI-](#) (b) (6)). In the case of intracerebral hemorrhage in the setting of thrombolytic therapy, although role for donanemab cannot be ruled out, thrombolytic therapy was a likely risk factor for the event of hemorrhage ([I5T-MC-](#) (b) (6)). In the case of subarachnoid hemorrhage with fatal outcome, this reviewer did not establish a role for donanemab in the event due to the concurrent event of fall from a ladder and past medical history of unsteadiness and falls ([I5T-MC-AACI-](#) (b) (6)).

In two of the three SAEs of hemorrhagic stroke, occurring in two subjects, a role for donanemab could not be ruled out. The cases are summarized here.

Hemorrhagic stroke, [I5T-MC-AACI-](#) (b) (6)

73 year-old female with past medical history of arteriosclerosis, hyperlipidemia, impaired glucose tolerance, ApoE ε3/ε4 genotype, with screening MRI showing superficial siderosis measuring 25 mm left frontal lobe who was hospitalized on Study Day 33 for the SAE of hemorrhagic stroke (severe) after presenting with olfactory hallucinations, paresis of the upper left limb, and left-sided hemianopia. On that day, she was also reported to have hypertension (mild, value not reported). She had received her second dose of donanemab the day before. At the study visit the day before, she had reported feeling weak and experienced vomiting at the site. Her blood pressure prior to dosing was noted to be elevated at 146/83 mmHg with a pulse rate was 72 beats per minute. Blood pressure visits from the previous two visits prior to receiving any treatment with donanemab were also elevated (142/82 mmHg and 146/88 mmHg). Concomitant medications at the time of hospitalization included duloxetine, menaquinone-7, metformin, phospholipids, ramipril, rosuvastatin, and troxerutin. Labs upon hospitalization were significant for a low platelet count of 145K/uL (reference range of 150-400). A CT of brain the same day showed an intracerebral hematoma measuring 60 x 40 mm in

right parieto-occipital lobe. The subject received treatment with hydroxyzinium, lactulose, mannitol, metoclopramide, calcium chloride dihydrate, potassium chloride, sodium acetate trihydrate, sodium chloride, and sodium citrate dihydrate. Two days later, a head MRI with contrast showed an intracerebral hematoma (also reported as a hemorrhage) of the right parietal area with morphology and size comparable to the previous CT examination. On Study Day 44, the subject was discharged from the hospital. On Study Day 71, the subject's study MRI showed initial identification of a hemorrhage measuring 52 mm in the right occipital lobe and previously identified superficial siderosis that was unchanged in size. On Study Day 106, an MRI showed the hemorrhage had decreased in size to 46 mm. On Study Day 150, the subject was reported to have recovered from the hemorrhagic stroke with sequelae of left sided homonymous hemianopia. The drug was withdrawn because of the event of hemorrhagic stroke. On Study Day 170, the MRI showed no change from Study Day 106.

Reviewer comment: A role for donanemab in the event of hemorrhagic stroke cannot be ruled out given that given that serious intracerebral hemorrhages greater than 1 cm have been reported in subjects treated with anti-amyloid antibodies.¹⁰⁵ The subject had elevated blood pressure on visits prior to receiving donanemab, which may have been a contributory factor for the SAE of hemorrhagic stroke. Additionally, the subject had presence of an ApoE ε4 allele, which is a risk factor for intracerebral hemorrhage, and superficial siderosis on screening MRI, which is a finding seen with cerebral amyloid angiopathy. Cerebral amyloid angiopathy is a risk factor for intracerebral hemorrhage.

Hemorrhagic stroke, I5T-MC-AACI- (b) (6)

A 78-year-old male with past medical history of transient ischemic attack, cerebrovascular accident, hypertension, hyperlipidemia, ε3ε4 genotype, normal pressure hydrocephalus (diagnosed on Study Day 225), shunt placement to the right parietal lobe (on Study Day 241) who developed a hemorrhagic stroke in the right superior parietal lobe on Study Day 402. The hemorrhagic stroke occurred 9 days after the 13th dose of donanemab. The subject recovered from the event on the same day. On Study Day 419, the subject experienced the SAE of seizure (severe). The subject recovered from the event of seizure on the same day. The screening MRI had been normal. The subject was not on any antithrombotics.

Reviewer comment: A role for donanemab in the event of hemorrhagic stroke cannot be ruled out given that intracerebral hemorrhages greater than 1 cm have been reported in patients treated with anti-amyloid antibodies; however, the subject had other risk factors for hemorrhagic stroke including presence of shunt, hypertension, hyperlipidemia, and the presence of an ApoE ε4 allele. This reviewer did not identify a role for donanemab in the SAE of seizure given the recently preceding event of hemorrhagic stroke, which may have been contributory to

¹⁰⁵ Leqembi. Labeling-Prescribing Information. Drugs@fda.gov. Action date July 6, 2023. Accessed August 24, 2023.

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the event of seizure.

For the SAE of intracerebral hemorrhage, a fall on the day of the SAE may have been a contributory factor (I5T-MC-AACI- (b) (6)). The case is summarized here.

Intracerebral hemorrhage, I5T-MC-AACI- (b) (6)

79 year-old male with past medical history of atrial fibrillation, coronary artery disease, hypertension, hyperlipidemia, ApoE ε3/ε4 carrier, who developed symptomatic ARIA-E (moderate) on Study Day 31 and then developed the SAE of intracerebral hemorrhage (severe) on Study Day 74, the same day as a fall. The AE of ARIA-E occurred on the same day as the second dose of donanemab, and the subject experienced the symptom of confusion. On Study Day 67 (unscheduled visit), an MRI showed as initial identification mild ARIA-E in the left and right cerebellum, left and right parietal lobes, and right frontal lobe and an initial identification of lacunar infarct in the right cerebellum which was reported as an AE of mild cerebellar infarction. On Study Day 74, the subject lost balance and fell to the sidewalk, which occurred 17 days after the 3rd dose. He experienced decreased vision in his left eye. A CT scan without contrast obtained on the same day as hospitalization showed right occipital lobe intraparenchymal hemorrhage with rupture into the right lateral ventricle, and mild ventriculomegaly without overt hydrocephalus. On Study Day 80, the subject was transferred to a rehab facility where he continued to experience decreased vision in his left eye. A follow up study MRI on Study Day 130 mild severity of ARIA-E, with increased size in the left and right cerebellum, left and right parietal lobes, right occipital lobe, and right frontal lobe, and initial identification of a macrohemorrhage of 29 mm in right occipital lobe. The clinical symptom of confusion associated with ARIA-E was ongoing at the time of the data cutoff. The subject had been on apixaban at the time of the ARIA-E event; however, this was stopped two days after the event (Study Day 33).

Reviewer comment: Although a role for donanemab cannot be ruled out, given that intracerebral hemorrhage have been reported in patients treated with anti-amyloid antibodies, the fall that subject experienced on the same day as the intracerebral hemorrhage is a potential risk factor. Additionally, the subject had presence of an ApoE ε4 allele, which is a risk factor for intracerebral hemorrhage.

The remaining two SAEs of subarachnoid hemorrhage reported in the all-donanemab pool were reported in the same subject. The case is summarized here.

Subarachnoid hemorrhage, I5T-MC-AACI- (b) (6)

70 year-old male with past medical history of AD, coronary artery disease, myocardial infarction, chronic kidney disease, hypertension, hyperlipidemia, gastroesophageal reflux

disease, B12 deficiency, chronic anemia, history of alcohol abuse, screening MRI which showed superficial siderosis measuring 17 mm (right frontal) who was hospitalized for the SAE of subarachnoid hemorrhage on Study Day 152 (severe) and for a second episode again on Study Day 176 (severe). On the day of hospitalization for the first episode of subarachnoid hemorrhage, the subject experienced dizziness and fell from a golf cart and was taken to the hospital. The subject was intubated on the way to the hospital and received ketamine. Upon arrival at the hospital, the subject was reported to have a Glasgow Coma Scale score (GCS) of 3T and was noted to be hypertensive but hemodynamically stable. The last dose of donanemab prior to the first SAE of subarachnoid hemorrhage was 10 days before (5th dose). On Study Day 154, a CT of the head without contrast showed mild right parietal and left frontal cortical sulcal subarachnoid hemorrhage, atrophy and chronic ischemic microvascular disease. Treatment included admission to the intensive care unit and initiation of a nicardipine drip for treatment of hypertension. The following day, the subject was extubated. A repeat CT scan of the brain without contrast two days later was reported to show a slight interval decrease in scattered areas of subarachnoid hemorrhage. A CT of the head without contrast was reported to show a mild subarachnoid hemorrhage within the right parietal and left frontal lobes, slightly more prominent than on the prior study, with possible small quantity of subarachnoid hemorrhage within the frontal lobe. A carotid duplex performed the following day was reported to show no hemodynamically significant atherosclerotic stenosis. The subject was discharged the same day (Study Day 155) and was taken off aspirin and was advised to have a repeat CT of the head in two weeks. On Study Day 176, the subject's wife found the subject confused and disoriented, and the subject was taken to the hospital. He was diagnosed with a second serious adverse event of subarachnoid hemorrhage (per report, this was confirmed to be two separate episodes). A CT angiogram the same day showed areas consistent with acute hemorrhagic contusions and small amount of subarachnoid hemorrhage in the left frontal lobe. The subject was discharged two days later. A repeat CT scan 17 days later was reported to be stable. The study drug was interrupted due to the SAE of subarachnoid hemorrhage. Concomitant medications before the first subarachnoid hemorrhage included acetylsalicylic acid (81 mg daily), atenolol, atorvastatin, cholecalciferol, cyanocobalamin, diazepam PRN, multivitamins, and omeprazole. Ten days before the development of the first SAE of subarachnoid hemorrhage (Study Day 142), the subject was noted to have elevated blood pressure (140/78 mmHg) and a heart rate of 59 beats per minute, with a normal temperature (36.3 degrees Celsius).

The most recent MRI prior to the first SAE of subarachnoid hemorrhage was on Study Day 95 and showed superficial siderosis of 17 mm (stable from screening). The next study MRI was on Study Day 213 and showed moderate ARIA-E (right parietal and right occipital), increase in size to right frontal superficial siderosis (50 mm), and 3 new areas of superficial siderosis (right frontal, 18 mm; right parietal, 19 mm; and left frontal, 55 mm). An MRI on Study Day 239 reported resolution of ARIA-E and stabilization of the superficial siderosis. The subject was considered recovered from both SAEs of subarachnoid hemorrhage on this day and donanemab

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was resumed on Study Day 247.

Other adverse events reported by the subject during the study included asymptomatic ARIA-E (mild, from Study Day 365 to 487) and superficial siderosis (moderate, starting on Study Day 365, outcome of the AE at the time of the data cutoff: not recovered).

Reviewer comment: The subject had risk factors for the development of subarachnoid hemorrhage include a preceding event of fall, history of hypertension, and concomitant therapy with aspirin.

This reviewer did not establish a role for donanemab in the five SAEs of subdural hematoma. In all of the cases, the SAE of subdural hematoma was preceded by potential risk factors, including fall (I5T-MC-AACI- (b) (6) I5T-MC-AACG- (b) (6) and I5T-MC-AACI- (b) (6)), trauma to head (I5T-MC-AACI- (b) (6) MRI finding 6 days after bumping his head on a window while walking; asymptomatic), and syncopal event (I5T-MC-AACI- (b) (6)).

One SAE of extradural hematoma was reported in the one subject who also experienced an SAE of subdural hematoma (I5T-MC-AACG- (b) (6)). In this case, this reviewer did not identify a role for donanemab given a preceding event of fall, which was a likely risk factor.

This reviewer also identified one subject with intracerebral hemorrhages that started more than 57 days after the last dose of donanemab; however, the intracerebral hemorrhages had ARIA occurring at the same time as the intracerebral hemorrhages, and the ARIA events had started within 57 days of the last dose of donanemab (I5T-MC-AACI- (b) (6)). The case is discussed here.

Intracerebral hemorrhages (noted on imaging), also reporting the SAE of Subarachnoid hemorrhage, I5T-MC-AACI- (b) (6)

A 69-year-old female subject homozygous for ApoE ε4, with past medical history of hyperlipidemia, on aspirin 325 mg daily, who developed severe ARIA-E on Study Day 569 (22 days after the first dose of donanemab), intracerebral hemorrhage of 11 mm on Study Day 625 (identified on a follow-up MRI along with ARIA-E, ARIA-H microhemorrhage, and ARIA-H superficial siderosis), a serious adverse event of subarachnoid hemorrhage on Study Day 645, and an additional intracerebral hemorrhage of 85 mm on Study Day 703 (also in the presence of ARIA-E, ARIA-H microhemorrhage, and ARIA-H superficial siderosis). On Study Day 569, 22 days after her first dose of donanemab, she reported severe ARIA-E (noted on MRI to occur bilaterally in the occipital, parietal, and temporal lobes and in the left frontal lobe). The ARIA-E was symptomatic (mild headache). Additionally on the same MRI, radiographically mild ARIA-H microhemorrhage (one new microhemorrhage with a total of three microhemorrhages on MRI), and radiographically moderate superficial siderosis (increased in size in the right parietal lobe

from 15 to 20 mm) were identified. The preceding MRI (Study Day 526, while the subject was on placebo) had noted the initial identification of superficial siderosis (15 mm, right parietal lobe) and focal lesions of white matter disease (present since screening MRI). On Study Day 597, the AE of superficial siderosis (mild) was reported. An MRI on this day showed mild ARIA-E in the bilateral occipital and temporal lobes. ARIA-E noted on the previous MRI in the right parietal lobe was noted as decreased in size. Greater than 10 new microhemorrhages (total 15) were reported as well as increase in size of superficial siderosis in the right parietal lobe (45 mm) and the development of superficial siderosis in the right temporal lobe (30 mm).

On Study Day 625, the subject's MRI showed macrohemorrhage measuring 11 mm in the left frontal lobe, moderate ARIA-E in the bilateral frontal and temporal lobes, right occipital and parietal lobes, with presence of >10 new microhemorrhages (total 31), and superficial siderosis increased in size in the right parietal lobe (75 mm) and right temporal lobe (50 mm), and new superficial siderosis in the right frontal lobe (50 mm).

On Study Day 645, the subject was hospitalized for the SAE of subarachnoid hemorrhage. She presented to the hospital with an elevated systolic blood pressure of 185 (units not specified). The subject denied any history of head injury, fall, or trauma that preceded the SAE. The mean blood pressure over seven study visits in the six months preceding the subarachnoid hemorrhage was 120/71 mmHg (range: systolic 108 to 136 mmHg and diastolic 66 to 77 mmHg). An MRA performed the following day did not show any aneurysm. The subject was noted to have left-sided hemiparesis. Corrective treatment included physical therapy and antihypertensives. The subject was discharged to home 35 days later and was reported to have improved with outpatient rehab.

On Study Day 703, an MRI showed presence of macrohemorrhages ([85 mm] in right frontal lobe [initial identification] and unchanged in size at left frontal lobe). The MRI result also showed severe ARIA-E at right frontal and parietal lobes as it decreased in size, presence of 3 new microhemorrhages (total 34), superficial siderosis that was increased in size in right parietal lobe (95 mm), right temporal lobe (75 mm), and right frontal lobe (125 mm), and newly identified superficial siderosis in the left frontal lobe (80 mm). Bilateral frontal subdural hematomas were also noted (initial identification). On Study Day 731, an MRI showed resolution of ARIA-E and unchanged superficial siderosis, microhemorrhages and macrohemorrhages, and increase in size of subdural hematoma in bilateral frontal lobes. On Study Day 736, the subject was permanently discontinued from the study drug because of the SAE of subarachnoid hemorrhage.

Reviewer comment: The subject had risk factors for the development of intracerebral hemorrhage including ApoE ε4 allele, daily use of aspirin 325 mg, and superficial siderosis on MRI prior to therapy with donanemab, which has been associated with cerebral amyloid angiopathy, which is a risk factor for intracerebral hemorrhage. Whether elevated blood

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pressure was contributory to the events of intracerebral hemorrhage is unknown, as the blood pressure elevation noted in the ER upon presentation for the subarachnoid hemorrhage may have been a compensatory effect for the event of hemorrhage. The subarachnoid hemorrhage may also have been related to the macrohemorrhage that preceded it with bleeding leaking into the subarachnoid space.^{106,107}

Cerebral infarction/Cerebrovascular Accident/Ischemic Stroke

This reviewer identified 15 SAEs related to the topic of cerebral infarction/cerebrovascular accident/ischemic stroke occurring in 14 subjects. Preferred terms included cerebrovascular accident (n=6), ischemic stroke (n=5), cerebral infarction (n=3), and fall.

In five cases, this reviewer did not establish a role for donanemab as the events occurred more than 80 days after the last dose of donanemab.¹⁰⁸

Two of the cases are discussed in the deaths section of this review ([I5T-MC-AACI-](#)(b) (6) and [I5T-MC-AACI-](#)(b) (6)).

Three cases of cerebral infarction are summarized here.

Cerebral infarction, I5T-MC-AACI-(b) (6)

74 year-old female with hypertension, ApoE ε4/ε4 carrier, who was diagnosed with the SAE of ARIA-H (moderate) and the AE of ARIA-E (mild) on Study Day 163 and developed the SAE of cerebral infarction (verbatim term: acute right occipital infarct) on Study Day 198. A screening MRI showed 2 microhemorrhages and a lacunar infarct in the bilateral deep grey matter. On Study Day 21, an MRI showed a lacunar infarct in the right occipital lobe which was reported as an adverse event (mild). On Study Day 56, an MRI showed ARIA-H and lacunar infarcts unchanged in size. On Study Day 163, 21 days after the 5th dose, an MRI showed 7 new microhemorrhages (total of 9), superficial siderosis of 4 mm in the right frontal lobe, moderate ARIA-E in the left and right frontal, occipital lobes, left parietal and right temporal lobes. The SAE of moderate ARIA-H and the AE of mild ARIA-E were reported on this day. The study drug was interrupted because of ARIA and then was permanently discontinued on Study Day 193 because the subject had met dose stopping criteria. On Study Day 198, an MRI showed the new

¹⁰⁶ Subarachnoid hemorrhage. Johns Hopkins Medicine. <https://www.hopkinsmedicine.org/health/conditions-and-diseases/subarachnoid-hemorrhage#:~:text=A%20subarachnoid%20hemorrhage%20means%20that,the%20brain%20bursts%20and%20leaks> Accessed February 7, 2024.

¹⁰⁷ Wang J, Wang D, Bian L. et al. Subarachnoid extension and unfavorable outcomes in patients with supratentorial intracerebral hemorrhage. BMC Neurol 2023 23; 46. <https://doi.org/10.1186/s12883-023-03087-9>

¹⁰⁸ I5T-MC-AACG-(b) (6) I5T-MC-AACI-(b) (6) I5T-MC-AACI-(b) (6) I5T-MC-AAC-(b) (6) and I5T-MC-AACI-(b) (6)

finding of right occipital infarct (considered non-serious at the time) and a small focus of diffusion restriction in right occipital lobe, ARIA-E present and decreasing in right frontal, right occipital, left occipital; 9 ARIA-H microhemorrhages (2 right occipital, 2 right parietal, 1 left temporal, 1 left frontal, 3 left parietal); superficial siderosis present (right frontal 4 mm) and unchanged 5mm lacunar infarct and 3mm right occipital lacunar infarct. The subject's exam that day was considered stable. Corrective treatments were not needed per the investigator. Fourteen days later, a carotid ultrasound showed bilateral stenosis (20-49%). The right internal carotid artery showed moderate heterogenous irregular plaque and the left internal carotid artery showed moderate heterogenous smooth plaque. Transcranial doppler showed that all vessels ultrasounded were within normal limits. The subject was considered to have recovered from the SAE of cerebral infarction on the same day.

Reviewer comment: The cerebral infarction occurred in the same location as ongoing ARIA-E and ARIA-H. Whether ARIA may have played a role in the SAE of cerebral infarction is unknown. The subject had risk factors for cerebral infarction including lacunar infarct on screening MRI and past medical history of hypertension. The presence of ApoE ε4 alleles, a history of microhemorrhages, and development of superficial siderosis prior to the event may be suggestive of CAA, which may have ischemic manifestations, including infarcts.¹⁰⁹

Fall, I5T-MC-AACI- (b) (6)

An 85 year-old male with past medical history of gait instability, hypertension, hyperglycemia, ApoE ε3/ε3 carrier, with encephalomalacia on screening MRI, who was hospitalized for the SAE of fall (moderate) on Study Day 652, 39 days after the 3rd infusion. A carotid ultrasound performed the same day showed extensive shadowing plaque in the right carotid bulb extending into internal carotid arterial with an estimated stenosis of greater than 70% but less than near occlusive, and in the left carotid system estimated stenosis of less than 50%.¹¹⁰ An MRI obtained on Study Day 624 (28 days prior to the SAE of fall) demonstrated moderate ARIA-E located in the right temporal (non-hippocampal) and right occipital lobes and four cortical infarcts (measuring 19 mm [right parietal], 11 mm [right frontal], 7 mm [right frontal], and 5 mm [right frontal]).¹¹¹ Treatment with donanemab was interrupted because of ARIA-E. An MRI obtained on Study Day 653 showed evolving late acute and subacute infarcts in the medial right postcentral gyrus and superior parietal lobule without associated mass effect or hemorrhage, and flair changes in right temporal-occipital area that had progressed when compared to the previous MRI. A central read of the MRI on Study Day 653 reported ARIA-E (moderate), right temporal non-hippocampal, left temporal non-hippocampal, right parietal, left parietal, and right occipital, increased in size compared to the prior MRI on Study Day 624. The previously

¹⁰⁹ Reijmer YD, van Veluw SJ, Greenberg SM. Ischemic brain injury in cerebral amyloid angiopathy. J Cereb Blood Flow Metab. 2015; 36:40-54. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4758563/>

¹¹⁰ Noted in the Applicant's response dated October 10, 2023, to an information request dated October 2, 2023.

¹¹¹ Noted in the Applicant's response dated October 3, 2023, to an information request dated October 2, 2023.

reported encephalomalacia and cortical infarcts were unchanged in size.¹¹² A screening MRI was reported to show encephalomalacia in the right temporal, non-hippocampal location. A centrally read MRI on Study Day 676 (obtained 24 days after the SAE of fall) showed presence of ARIA-E in right occipital lobe, less than 5 cm and decreased in size, mild in severity and an initial identification of 5 new microhemorrhages (2 left parietal, 1 right parietal, 1 right occipital, and 1 right temporal non-hippocampal).¹¹³ An MRI of the brain 39 days later showed ARIA-E, decreased in size and presence of two initial microhemorrhages for a total of seven microhemorrhages (2 left parietal, 1 right parietal, 3 right occipital, and 1 right temporal non-hippocampal), and cortical infarcts unchanged in size.

Reviewer comment: Risk factors for cerebral infarction exist in the case including carotid artery stenosis, hypertension, and hyperglycemia. Additionally, the subject was also noted to have encephalomalacia on screening MRI, which may be indicative of prior cerebral infarction. The subject was noted to have multiple cerebral infarctions on the same MRI as initial identification of moderate ARIA-E. Whether ARIA may have played a role in the cerebral infarctions is unknown. The subject's history of unsteadiness and event of ARIA-E at the time of the fall may have been contributory to the event of fall.

Intracerebral Infarction, I5T-MC-AACI- (b) (6)

76 year-old male with past medical history of hypercholesterolemia, hypertension, diabetes mellitus type 2, seizure, ApoE ε3/ε3 carrier who experienced the SAE of intracerebral infarction (mild) on Study Day 9 (9 days after the 1st dose of donanemab). Concomitant medications included acetylsalicylic acid and clopidogrel. An MRI of the brain performed on Study Day 9 showed an abnormal right parietal lobe gyri form and T2 signal intensity suggestive of sequelae of ischemic event. On the same day, the MRI findings were reported as an SAE of mild cerebral infarction (verbatim term: subacute right occipital cortical infarct). The subject was reported to have not experienced any symptom and was considered to be recovered from the event on the same day. A carotid ultrasound was performed (date not specified) and no findings or changes in health were reported. A physical exam performed 7 days later was notable for a slower response on stereognosis in the left hand compared to the right. An echocardiogram 14 days later showed moderate left ventricular systolic dysfunction, grade 1 diastolic dysfunction, an ejection fraction of 42%, and hypokinesia to the basal inferior, basal inferolateral, basal anterolateral, mid inferior, mid inferolateral, and mid anterolateral wall. The subject was started on clopidogrel. Blood pressure was noted to be normal at baseline (101/61 mmHg) and on Study Day 50 (116/67 mmHg).

¹¹² Noted in the Applicant's response dated December 11, 2023, to an information request dated December 4, 2023.

¹¹³ Presence of microhemorrhages are noted on page 8 of the Applicant's response dated October 3, 2023, to an information request dated October 2, 2023.

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Reviewer comment: A role for donanemab in the event of cerebral infarction cannot be established given the subject's past medical history of hypertension, hypercholesterolemia, and diabetes, which are potential risk factors for cerebral infarction.

In the remaining SAE of cerebral infarction, this reviewer did not identify a role for donanemab, as the infarction occurred in the setting of a new diagnosis of B-cell lymphoma, which was a possible risk factor for the event (I5T-MC-AACI- (b) (6)).

This reviewer did not identify a role for donanemab in the two SAEs with preferred term of cerebrovascular accident, because of past medical history as a likely risk factor in one case (I5T-MC-AACI- (b) (6) coronary artery disease, hypertension, hyperlipidemia, and diabetes mellitus) and lack of information in the second (I5T-MC-AACI- (b) (6) lacking information related to diagnosis or treatment).

This reviewer did not identify a role for donanemab in the one SAE with preferred term of Ischemic stroke because of the potential risk factor of fall that the subject had sustained two days prior to the event (I5T-MC-AACI- (b) (6)).

In the remaining case of ischemic stroke (left thalamic ischemic stroke), the reviewer did not establish a role for donanemab in the event as the subject had underlying risk factors including past medical history of hypertension, hyperlipidemia, and coronary artery disease (I5T-MC-AACI- (b) (6)).

Seizure

The reader is referred to Section 8.5.3 for a discussion of seizure including [narratives](#) of serious cases.

Infusion Related Reaction

This reviewer identified six SAEs of infusion related reaction occurring in six subjects in the all-donanemab pool (0.2%, [6/2802]). A role for donanemab was likely in all cases.

Infusion related reaction, I5T-MC-AACG- (b) (6)

A 75-year-old female with history of AD, hyperlipidemia, hypertension, aortic atherosclerosis, gastroesophageal reflux disease and high titer of treatment-emergent anti-drug antibodies (TE-ADA) (>20,480) who experienced a severe infusion reaction, characterized by the development of chest pressure that started within 6 hours after the fourth dose of donanemab on Study Day 93. Two days later (Study Day 95), the subject was admitted to the hospital with chest pressure, negative troponins, and nonspecific ecg findings. The subject also experienced mild dizziness,

mild asthenia, mild reflux, and mild urinary tract infection on the same day. The subject was treated with acetylsalicylic acid 324 mg chewed once, sodium chloride 1000 ml intravenously, magnesium hydroxide simethicone 50 mg orally once, and famotidine 20 mg intravenously once. The subject had elevated lipase levels (number not reported). A CT of the abdomen/pelvis with contrast showed atherosclerotic vascular calcifications, including in the coronary arteries. The chest x-ray showed no focal consolidation, no pleural effusion or pneumothorax, and a normal cardiomeastinal silhouette. The following day (Study Day 96), rest and stress myocardial perfusion scintigraphy with single-photon emission computed tomography showed no scintigraphic evidence of myocardial infarction or stress induced myocardial ischemia, normal left ventricular ejection fraction and no regional wall motion abnormality. The event of infusion reaction was assessed as a delayed infusion reaction. On that day, the subject recovered from the SAE of infusion related reaction and from the AEs of headache, dizziness, and asthenia. The AE of gastroesophageal reflux disease was not resolved. No action was taken with the study drug in response to the SAE of infusion related reaction. The subject went on to receive another dose of donanemab prior to completing the double-blind treatment period and no AEs of infusion related reaction were reported.

Also of note, on Study Day 29, anti-drug antibodies were detected at a titer of 1:160. On Study Day 93 (after the fourth dose of donanemab), the titer levels had increased to 1:81,920. On Study Day 120, the anti-drug antibody titer level had decreased to 1:40,960. On the same day, she discontinued the study drug due to the AE of mild nausea. She also experienced mild dizziness on that day. She was reported to have recovered from both the nausea and the dizziness that same day. On Study Day 175, the ADA titer had decreased to 1:5120 and by Study Day 364 to 1:2560.

Reviewer comment: The symptom of chest pressure appears consistent with a diagnosis of infusion related reaction given temporal association with donanemab infusion and lack of other etiologies including a normal chest x-ray and lack of evidence of cardiac ischemia on stress testing. A role for donanemab in the event of infusion related reaction is likely given temporal association.

Infusion related reaction, I5T-MC-AACI- (b) (6)

81-year-old male with history of drug hypersensitivity (allergy to sulfa, opium, and polysporin), seasonal allergy, and allergic rhinitis who developed the SAE of moderate infusion related reaction characterized by low blood pressure of 90/40 mmHg (135/65 mmHg before infusion), chest pain, nausea/vomiting, chills, malaise, and difficulty breathing/dyspnea that started within 6 hours of his second dose of donanemab (Study Day 34). He was hospitalized and discharged the following day. The subject went on to receive two more infusions and no further AEs were reported.

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Reviewer comment: The case appears consistent with a diagnosis of anaphylaxis given symptoms of dyspnea and hypotension. A role for donanemab in the event of anaphylaxis is likely based on temporal association. Given absence of reoccurrence with two additional exposures, this case appears consistent with a non-IgE mediated reaction.

Infusion related reaction, I5T-MC-AACI- (b) (6)

73-year-old female with history of hypertension, hypercholesterolemia who experienced the SAE of moderate infusion related reaction, characterized by the development of a hot flushed feeling and nausea 6-7 minutes into the fourth dose of donanemab administration. The infusion was interrupted. The subject was reported to experience low blood pressure (value not reported), headache, nausea/vomiting, chills, and myalgia. She received treatment with ondansetron and epinephrine on that day. She also received paracetamol and cetirizine as prophylaxis on that day and the following day. The SAE was reported as resolved that day and the study drug was permanently discontinued because of the SAE of infusion related reaction. Of note, during the third dose, the subject developed lightheadedness and nausea 11 minutes into the infusion and the study drug was interrupted. The study drug was resumed and the subject was noted to have a drop in blood pressure (value not reported).

Reviewer comment: The case appears consistent with a diagnosis of infusion related reaction. A role for donanemab in the event of infusion related reaction is likely based on temporal association.

Infusion related reaction, Pneumonia, Atrial fibrillation, I5T-MC-AACG- (b) (6)

This is a 70-year-old female with history of drug sensitivity, anaphylactic reaction (trigger not reported), asthma, atrial fibrillation, chronic kidney disease, diabetes mellitus type 2, and colon cancer who experienced the SAEs of infusion related reaction (severe), pneumonia of moderate severity, and atrial fibrillation of mild severity, which started on the same day as administration of the fourth dose of donanemab (Study Day 122). The subject also developed hypertension and nausea within 5 minutes of the start of the fourth infusion. Vital signs included blood pressure 220/70 mmHg, heart rate 72, and respirations 26. Concomitant medications included metformin, amlodipine, calcium carbonate, glimepiride, irbesartan, magnesium, metformin, metoprolol, and procaterol. The subject was reported to then become hypotensive in the act of standing (systolic blood pressure of 80 mmHg). The subject received a normal saline bolus and oral diphenhydramine. Fifteen minutes after hypotension was recorded, the blood pressure was recorded at 140 mmHg. The subject felt shortness of breath, nausea, and anxiety. Five minutes later, the blood pressure was 180/75 mmHg. The subject was taken to the ER and developed atrial fibrillation with rapid ventricular response (heart rate in the 150s). Abnormal labs in the ER showed low platelet count, low lymphocytes, low potassium, elevated creatinine, decreased glomerular filtration rate, elevated glucose, and elevated lactic acid (platelet count

135×10^3 [150-400], lymphocytes auto 0.5×10^3 [1.0-4.8], potassium (K) 3.4 mmol/L [3.5-5.3], creatinine 1.2 mg/dL [0.5-1.1], estimated GFR 45L (≤ 60 ml/min), glucose 272 mg/dL [fasting, less than 100], and lactic acid 4.0 mmol/L [0.5-2.2]). She was started on a diltiazem drip for the atrial fibrillation and the dose of metoprolol succinate was increased. A CT scan of the chest showed the possibility of pneumonia versus an infiltrate or reaction to the drug. The subject was diagnosed with the SAE of pneumonia and was started on an antibiotic (name of antibiotic not reported). The metformin was discontinued because of lactic acidosis. Three days later (Study Day 125), the potassium was normal (4.1 mmol/L). The following day, the creatinine, lactic acid, lymphocyte count, and platelet count were normal (creatinine 1.0 mg/dL, lactic acid 1.9 mmol/L, lymphocyte count 1.1×10^3 , and platelet count 151×10^3). She was discharged on levofloxacin and diltiazem. She was also started on apixaban by her cardiologist. The SAEs of infusion related reaction and atrial fibrillation were considered recovered on Study Day 126 and the SAE of pneumonia on Study Day 130. On Study Day 148, the subject discontinued from study drug because of the SAE of infusion related reaction.

Reviewer comment: The case appears consistent with anaphylaxis given hypotension and symptoms of dyspnea. A role for donanemab in the SAE of infusion reaction is likely given temporal association of symptoms with infusion. The case is notable because of the documented elevated blood pressure of 220/70 mmHg and low blood pressure (systolic of 80 mmHg upon standing) that occurred at the time of the infusion related reaction. A role for donanemab in the SAEs of atrial fibrillation and pneumonia cannot be established given the concurrent event of infusion related reaction, which was likely contributory to the SAEs of atrial fibrillation and pneumonia. Additionally, the subject's history of atrial fibrillation was also likely contributory to the development of atrial fibrillation after the infusion. The SAE of pneumonia may have also been contributory to the event of atrial fibrillation.

Infusion Related Reaction, IST-MC-AACI- (b) (6)

77-year-old female with hypertension, hyperlipidemia, and history of eyelid ptosis who developed the SAE of infusion related reaction (mild in severity) on the day of the first dose of donanemab.¹¹⁴ The subject reported the symptom of eyelid edema within 30 minutes of the end of study drug administration. The subject was taken to the ER for stroke evaluation after reporting worsening of eyelid ptosis, unsteady gait, and dizziness. An MRI of the brain showed no acute infarct or hemorrhage and symptoms were considered secondary to chronic ischemic changes and edema in the left masticator space. The symptoms of eyelid swelling resolved on the same day without treatment. She received a second dose of study drug and did not report any AEs related to infusion related reaction.

Reviewer comment: A role for donanemab in the SAE of infusion related reaction is likely given

¹¹⁴ The AE of Localized edema was updated to the SAE of infusion related reaction in the 90-Day Safety Update, submission date August 17, 2022.

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temporal association of symptom with infusion. This likely represents a non-IgE mediated reaction given occurrence after the first dose of donanemab.

Infusion related reaction, I5T-MC-AACI- (b) (6)

60 year-old female with past medical history of hypertension, migraines, allergies (aspirin, Levaquin, prednisone, Ativan, fluoxetine, Nubain, Vicodin, tape, yellow dyes, and MSG), who experienced the SAE of infusion related reaction (severe) during administration of the fourth dose of donanemab (Study Day 85). The subject experienced elevated blood pressure (blood pressure not reported), fear/panic, nausea/vomiting, difficulty breathing/dyspnea, and erythema on face, eyelid, nose, cheek, and ear. The infusion was stopped within 10 minutes of initiation. Fifteen minutes after stopping the infusion, the blood pressure was 90/56 and the pulse rate was 68 beats per minute (predose, the blood pressure was 136/81 mmHg and sitting pulse rate was 64 beats/min) and the respiratory rate was 16, and oxygen saturation was 98%. Approximately 30 minutes later, the blood pressure had increased to 150/85 mmHg. Treatment medications included diphenhydramine hydrochloride, methylprednisolone sodium succinate, ondansetron and aluminum hydroxide/magnesium, and trisilicate/sodium alginate. The event was considered recovered on the same day. The drug was permanently discontinued due to the event.

Reviewer comment: The case is consistent with infusion related reaction and a role for donanemab is likely given temporal association with the symptoms of infusion. Also, given the symptoms of reduced blood pressure and respiratory symptoms, the event is consistent with anaphylaxis.

Additional Cases with SAEs Related to Infusion Related Reactions

This reviewer identified three additional cases with SAEs where an infusion related reaction was likely contributory (acute myocardial infarction, I5T-MC-AACI- (b) (6) angina pectoris, I5T-MC-AACI- (b) (6) and respiratory distress, I5T-AACI- (b) (6)). The cases are summarized here.

Acute myocardial infarction, I5T-MC-AACI- (b) (6)

A 73 year-old female with past medical history of hypertension, hyperlipidemia, who experienced the SAE of acute myocardial infarction (verbatim term NSTEMI with atypical chest pain) during administration of the third dose on Study Day 56. The infusion was stopped 5 minutes after initiation. The subject experienced chest pain, elevated blood pressure (217/117 mmHg), fear/panic, mucocutaneous erythema and rash in the chest, difficulty breathing/dyspnea. The blood pressure prior to the dose was 150/80 mmHg with a heartbeat of 62 beats per minute. Oxygen saturation was 98-99% 11 minutes after initiation of the infusion.

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She received oxygen and normal saline. She was admitted to the hospital for NSTEMI and received glyceryl trinitrate and acetylsalicylic acid for treatment. Her potassium level was 3.3 (units and reference range not reported). A left heart catheterization with ventriculogram was performed on the same day and showed 30-40% occlusion of left anterior descending artery and an ejection fraction of 55-60% with mitral regurgitation. No stents were placed. The following day, the subject was noted to have elevated blood pressure (blood pressure value not reported) with troponins levels that were initially negative and then rose to 0.40, then 0.38 and then 0.29 (units and reference range not reported). The subject was discharged the following day and was considered recovered from the event. The subject was discontinued from the study.

Reviewer comment: The case appears consistent with hypertensive emergency given occurrence of NSTEMI in the setting of elevated blood pressure. A role for donanemab is likely given that symptoms started during an infusion. The subject's past medical history of hypertension and hyperlipidemia were likely contributory to the event of hypertension and NSTEMI.

Angina pectoris, I5T-MC-AACI- (b) (6)

A 78 year-old male with history of coronary artery disease, chronic obstructive pulmonary disease, hypertension, seasonal allergy who developed the SAE of angina pectoris (moderate) during the fifth dose of donanemab within 10 minutes of the start of the infusion (Study Day 114). The blood pressure was 168/108 mmHg, heart rate 91 beats per minute, and oxygen saturation 97% (predose the blood pressure was 139/78 mmHg, pulse rate 60 bpm and oxygen saturation 97%). The subject received oxygen and nitroglycerin sublingually and was taken to the hospital. He reported discomfort in the left side of his chest and diaphoresis. An ECG demonstrated no acute changes and high sensitivity troponins were negative. A metabolic panel and complete blood cell count were reported to be unremarkable. An echocardiogram showed normal left ventricular function and a chest x-ray showed no acute lung disease. The subject underwent a cardiac catheterization which was reported to show critical lesions in the mid right coronary artery and posterior descending artery. The subject underwent stenting to these lesions. The subject recovered from the SAE two days later. On Study Day 142, during administration of the 6th dose of donanemab, the subject developed the AE of infusion related reaction (moderate, verbatim term angina pectoris). Within 10 minutes of the initiation of the infusion, the subject developed chest pain, elevated blood pressure, dyspnea, diaphoresis, and flushing to the face. Prior to the infusion the blood pressure was 134/64 mmHg and pulse rate was 77 beats per minute. The study drug was permanently discontinued due to the AE of infusion related reaction. The subject recovered from the event on the same day.

Reviewer comment: A role for donanemab in the SAE of angina pectoris is likely given occurrence on two separate occasions of symptoms during donanemab infusion. The subject's history of coronary artery disease is a likely contributory factor to the SAE of angina pectoris.

Respiratory distress (I5T-AACI- (b) (6))

67 year-old female with medical history of AD who developed the SAE of respiratory distress (severe) within 5 minutes of initiation of the infusion for the third dose of donanemab (Study Day 118). The subject reported difficulty breathing during the infusion. During the episode, the blood pressure was 142/90 mm Hg, heart rate was 118 beats per minute and oxygen saturation was 82% (predose, the blood pressure was 122/76 mmHg, with a heart rate of 79 beats per minute). She was noted to be cyanotic and pale. The infusion was stopped and the subject was given epinephrine and methylprednisolone sodium succinate 120 mg. An ECG was reported to be unchanged from before. The subject was considered fully recovered within six hours of the start of the episode. Prior to the third infusion, the subject was reported to have experienced chest pain and a sense that she could not breath during the second infusion (Study Day 37) and was seen in the emergency department. No findings from the ER visit were reported.

Reviewer comment: A role for donanemab in the SAE of respiratory distress is likely given onset at the time of the donanemab infusion and occurrence of similar symptoms during a previous donanemab infusion.

This reviewer also notes an SAE of syncope where a role for donanemab could not be ruled out. The SAE occurred within two hours of the end of the infusion for the second dose of donanemab; however, a likely contributory factor in the case include hypotension prior to start of the infusion (predose blood pressure of 87/47 mm Hg) (I5T-AACI- (b) (6)).

This reviewer also notes one blinded case from Study AACQ that was submitted in a 7-day adverse event report after the 90-Day Safety Update on November 9, 2023, that involved a 71-year-old male who developed chest pain and shortness of breath, syncope, apnea, asystole, and pulselessness (Mfr #: US202311003008). The subject became arousable and was given fluids to increase blood pressure and transported to the emergency room. The subject was considered recovered the following day and was discharged from the hospital.

Other Hypersensitivity Events

This reviewer searched for serious cases belonging to the Hypersensitivity SMQ (Narrow), excluding infusion related reactions, occurring in the treatment period plus 57 days.

This reviewer identified ten SAEs within the Hypersensitivity SMQ occurring in ten subjects in the all-donanemab pool (0.4%, [10/2802]). Preferred terms included: anaphylactic reaction (n=4); and anaphylactic shock, drug eruption, hypersensitivity, infusion related hypersensitivity reaction, type iv hypersensitivity reaction, and urticaria (one each).

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The cases are summarized here.

Anaphylactic reaction, I5T-MC-AACI- (b) (6)

72-year-old female with PMH of AD, hypercholesterolemia, history of anaphylactic reaction (cefotiam hydrochloride and penicillin) who received her second dose of donanemab and within 5 minutes of starting the infusion developed difficulty breathing and palpitations on Study Day 29.¹¹⁵ The donanemab infusion was interrupted 15 minutes after starting, and she developed diarrhea, vomiting, weakness of the limbs, and hypotension. Her blood pressure was 88/57 mmHg and her heart rate was 93 beats per minute. Prior to the infusion, her blood pressure was 122/56 mmHg and her heart rate was 69 beats per minute. She was treated with epinephrine and calcium chloride/potassium/sodium chloride/sodium lactate that day and was admitted to the hospital overnight for observation. The SAE of moderate anaphylactic reaction was reported as resolved the following day and she was discharged from the hospital. The study drug was discontinued.

Reviewer comment: The case appears consistent with a diagnosis of anaphylactic reaction, given onset of vomiting and hypotension within minutes of a donanemab infusion. A role for donanemab is likely given temporal association.

Anaphylactic reaction, I5T-MC-AACI- (b) (6)

63-year-old female with history of AD, anxiety, migraine, hypothyroidism on levothyroxine who developed mucocutaneous urticaria, swelling and erythema of neck, throat and chest tightness, dry cough, and bronchospasm (noted on auscultation) 25 minutes after receiving the first donanemab infusion and was diagnosed with a moderate anaphylactic reaction. She was treated with diphenhydramine, epinephrine, methylprednisolone, and oral famotidine. Approximately one hour after starting the donanemab infusion, her blood pressure was 163/82 mmHg and heart rate was 68 beats per minute (prior to the infusion, blood pressure: 137/77 mmHg, heart rate: 83 beats per minute [bpm]) and the urticaria and bronchospasm had resolved. She was taken to the ER and an exam showed blood pressure of 164/70 mmHg, heart rate 96 bpm, respiratory rate of 20 breaths/minute, shallow breathing, and an area of erythema on her neck. No labs or other diagnostic tests were performed. She was discharged as recovered and prescribed diphenhydramine, prednisone, and an epinephrine pen as needed.¹¹⁶ The SAE was considered resolved on the same day, and she permanently discontinued from study drug and the study.

¹¹⁵ Narrative updated by the Applicant to include history of anaphylactic reaction in a response dated August 19, 2022, to an information request dated August 17, 2022.

¹¹⁶ Narrative updated by the Applicant in a response dated August 19, 2022, to an information request dated August 17, 2022, to specify that a second event of anaphylactic reaction was not experienced by the patient as originally described in the submission.

Reviewer comment: The case is consistent with anaphylaxis given onset of skin and mucosal involvement within minutes of exposure to the first infusion of donanemab and evidence of bronchospasm on exam.¹¹⁷ A role for donanemab in the SAE is likely given temporal association with onset of the AE and the donanemab infusion. The mechanism of action is likely non-IgE mediated given lack of previous exposure to donanemab.

Anaphylactic reaction, I5T-MC-AACI- (b) (6)

69 year-old female who experienced the SAEs of hypoxia and anaphylactic reaction during the fourth infusion on Study Day 632. The subject was reported to have been found unresponsive with agonal breathing, blue in the face, and slightly tremulous. The infusion was stopped 7 minutes after starting. Oxygen saturation was 60%. The subject was given oxygen, methylprednisolone, famotidine, and diphenhydramine. The subject was hospitalized for severe anaphylactic reaction and hypoxia. Vital signs upon arrive at the hospital included a blood pressure of 145/124, pulse 89 and oxygen saturation of 70%. The subject was noted to have difficulty breathing, dyspnea, wheezing, and cognitive changes. The subject improved and was discharged from the hospital on the same day.

Reviewer comment: The symptoms of unresponsiveness and hypoxia and wheezing in the setting of a likely allergen in the case are consistent with anaphylaxis.¹¹⁸ Given occurrence of symptoms during an infusion of donanemab, the SAE is likely related to donanemab infusion.

Anaphylactic Shock, I5T-MC-AACI- (b) (6)

This is a 71 year-old female with medical history of depression and AD, who experienced the SAE of anaphylactic shock (severe) on Study Day 562, during the first infusion of donanemab. The infusion was stopped 5 minutes after initiation. Symptoms started after one minute of infusion and included tingling sensation to the arms, irregular breathing, no reaction when addressed by name, and able to react to pain. Vital signs were not reported. The subject was hospitalized for the event and discharged on the same day. Information related to labs and corrective treatment were not reported. The event was considered resolved on the same day. Blood pressure prior to the infusion was 113/80 mmHg with a pulse rate of 68 beats per minute. Concomitant medications included donepezil and sertraline. The subject was discontinued from the treatment period due to the event.

¹¹⁷ Sampson H, Munoz-Furlong A, Campbell R, et al. Second symposium on the definition and management of anaphylaxis: summary report-Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network Symposium. J Allergy Clin Immunol 2006; 117: 391-397.

¹¹⁸ Sampson H, Munoz-Furlong A, Campbell R, et al. Second symposium on the definition and management of anaphylaxis: summary report-Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. J Allergy Clin Immunol 2006; 117:391-397.

Reviewer comment: Symptoms of end organ dysfunction (altered mental status) and respiratory compromise (irregular breathing) occurring in the setting of a likely allergen are consistent with anaphylaxis.¹¹⁹ Given the onset of the event at the time of the infusion, a role for donanemab in the SAE of anaphylactic shock is likely.

Anaphylactic reaction, I5T-MC-AACI- (b) (6)

75-year-old female with past medical history of drug intolerance (codeine, levofloxacin and sulfa), allergy to cats, eczema, seasonal allergic disorder, lactose intolerance, who developed generalized erythema (including the chest, abdomen, back, throat, lip, ear, and eyelid), chest tightness, tachycardia, elevated blood pressure, and nausea within 12 minutes into her 3rd donanemab infusion. The SAE was reported to be severe anaphylactic reaction and the infusion was interrupted. Her heart rate was 93 beats per minute and blood pressure was 171/99 mmHg 15 minutes after starting the infusion. She was given epinephrine, intravenous diphenhydramine, and a normal saline bolus. The SAE was considered resolved on the same day. She was given four doses of oral diphenhydramine to be taken every 6 hours and discontinued from the study drug and the study because of the SAE. Of note, she had experienced paresthesias on the same day as her second infusion of donanemab.

Reviewer comment: The case may represent anaphylaxis given onset within minutes of the infusion, involvement of the skin, and development of chest tightness. A role for donanemab in the SAE is likely given temporal association with onset of the AE and the donanemab infusion.

Infusion related hypersensitivity reaction, I5T-MC-AACI- (b) (6)

72 year-old male with who experienced the SAE of infusion related hypersensitivity (moderate) within 30 minutes of completing the second infusion of donanemab (Study Day 35). At the end of the infusion, the blood pressure was 107/65 mmHg and pulse rate was 67 beats per minute. Fifteen minutes later, the subject had a low blood pressure of 78/52 mmHg (the predose blood pressure was 111/64 mmHg with a pulse rate of 58 beats per minute), nausea, vomiting, chills, and rigors. Two minutes later, the blood pressure was 94/71 mmHg with a pulse rate of 87 beats per minute, and oxygen saturation in the 90's. Approximately 10 minutes later, the blood pressure had increased to 137/65 mmHg and pulse rate was 84 beats/min and oxygen saturation was 98%. In the emergency room, the subject's blood pressure was 115/73 mmHg and pulse rate was 92 beats/min, and the physical exam was normal. The subject denied chest pain, shortness of breath, rashes, or wheezing. He received 250 mL of normal saline, 25 mg of diphenhydramine intravenously, and 4 liters of oxygen. The subject recovered from the event

¹¹⁹ Sampson H, Munoz-Furlong A, Campbell R, et al. Second symposium on the definition and management of anaphylaxis: summary report-Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. J Allergy Clin Immunol 2006; 117:391-397.

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on the same day and the study drug was discontinued after the event.

Reviewer comment: The SAE of infusion related hypersensitivity reaction is likely related to donanemab given onset of the event during the infusion of donanemab. The case may also represent a case of anaphylaxis given the low blood pressure close to the time of infusion.

Urticaria, I5T-MC-AACI- (b) (6)

80 year-old male who reported the SAE of urticaria (mild) on the same day as the second dose of donanemab (Study Day 43). The subject reported red hives and itchiness during the infusion. The subject was noted to have small, less than six inches in diameter rash on the left arm, base of neck and chest and was diagnosed with urticaria. The subject was given oral diphenhydramine 25 mg prior to leaving the site. The subject recovered from the event a day later. The study drug was permanently discontinued because of the SAE.

Reviewer comment: A role for donanemab in the SAE of urticaria is likely given onset during infusion with donanemab.

Drug Eruption, I5T-MC-AACG- (b) (6)

A 73-year-old female with history of allergy to tetanus vaccine, drug hypersensitivity (ibuprofen; sulfonamides, gastrointestinal tolerance), and eczema who reported the SAE of drug eruption 9 days after the first infusion with donanemab (moderate in severity). The subject had generalized itching and erythematous rash/hives on her neck, trunk, and extremities. The rash was reported as an erythematous, blanching raised rash on her extremities and trunk with a pruritic pink and purple eruption on her neck and back that spread to her arms and legs. She denied any eye irritation, oral lesions, or vaginal irritation. She denied any new exposures to food, detergents, soaps, and other body care products. She was seen in the ER and treated with prednisone and triamcinolone cream and diagnosed with a drug eruption. In the ER, her blood pressure was 146/72 mmHg, heart rate of 66 bpm, temperature 97.8 degrees Fahrenheit, respiratory rate 18 breaths per minute, and peripheral oxygen capillary saturation of 99%. On Study Day 13, she had a normal urinalysis (no blood or protein on microscopic examination), normal blood urea nitrogen (BUN) (21mg/dL with normal range 6-24), normal creatinine (0.82mg/dL with reference range of 0.44-1.03), normal complete blood count (CBC) (white blood cell count (WBC) 7.6 x10⁹/L [3.5-11.0], hemoglobin 12.4g/dL [11.0-15.0], and platelets 219 x10⁹/L [150-400]). The differential on the white count included neutrophils 81.2%, lymphocytes 12.3%, monocytes 5.0%, eosinophils 1.0%, absolute eosinophil count 0.1 K/uL (0.0-0.5), and basophils 0.5% (no reference ranges provided). The subject was evaluated by a dermatologist who described the skin exam on Study Day 13 that included lichenoid plaques on the bilateral ventral forearms, distal arms, thigh and shins with clearing in the abdomen, back and face. The dermatologist assessment was "favor drug eruption."

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Concomitant medications included warfarin (started > 15 years ago), iron, estradiol, memantine, calcium carbonate + D3. She was started on prednisone 60 mg daily for four days and the event resolved on Study Day 30. She withdrew from the study drug because of the SAE of drug eruption.

Reviewer comment: The case appears consistent with a diagnosis of a delayed hypersensitivity reaction. A role for donanemab in the event of drug eruption is likely given temporal association of drug with onset of symptoms. Predisposing factors in the case likely included the subject's past history of drug hypersensitivities. The case appears consistent with a non-IgE mediated reaction given occurrence of the SAE after the first dose.

In one case with preferred term of hypersensitivity, this reviewer did not establish a role for donanemab as the subject was ultimately diagnosed with cellulitis in an event that started 73 days after the last dose of donanemab (I5T-MC-AACI- (b) (6)).

In the remaining case, a role could not be established because of a lack of information (Type IV hypersensitivity reaction, I5T-MC-AACI- (b) (6)). The subject was hospitalized for the SAEs of Confusional state (mild), Erythema (mild, verbatim term facial erythema), and Type IV hypersensitivity reaction (mild, verbatim term: Hospitalization due to delayed allergic reaction) 7.5 hours after the second infusion. An electroencephalogram (EEG) was planned to be conducted. The subject was discharged from the hospital two days later. Further information regarding labs, treatment, or results of additional tests were reported. The outcome of the event was considered recovered two days later. Four days after hospital discharge, an MRI of the brain did not show evidence of ARIA or other structural MRI abnormalities.

Comment: This reviewer found the coding of the verbatim term to the dictionary-derived term of Type IV delayed hypersensitivity reaction to be inaccurate based on the verbatim term reported. A role for donanemab cannot be established given lack of further details such as results of labs or additional tests such as results of an EEG.

Additional Cases Related to Anaphylaxis

This reviewer identified three additional cases related to the topic of anaphylaxis (syncope, I5T-MC-AACI- (b) (6) infusion related reaction, I5T-MC-AACI- (b) (6) and infusion related reaction, I5T-MC-AACI- (b) (6)). The cases of infusion related reaction are summarized in the Narratives section of Infusion Related Reactions. The case of syncope is summarized here.

Syncope, I5T-MC-AACI- (b) (6)

A 78-year-old male with history of asthma, diabetes mellitus type 2, hypertension, and tobacco use who developed SAE of syncope on Study Day 91, on the same day as the fourth dose of

donanemab. On Study Day 31, one day after receiving his second dose of donanemab, he experienced an AE of mild infusion related reaction, characterized by confusion, dizziness, and chills. The AE resolved two days later. On Study Day 63 and on the same day as his third infusion, he experienced a mild infusion related reaction, characterized by chills and shortness of breath. The infusion was interrupted on that day and received paracetamol and diphenhydramine. On Study Day 91, within five minutes of starting the fourth infusion, the subject passed out and was not responsive for three to five minutes. The subject's eyes were rolled back in his head, and no twitching, incontinence, or respiratory distress was observed. Blood pressure upon waking was 144/98 mmHg and heart rate was 89 beats per minute and oxygen saturation was 93% (preinfusion: blood pressure: 140/82 mmHg and heart rate: 83 beats per minute). By the time the subject had arrived in the ER, his symptom had resolved. He denied any associated symptoms of chest pain, abdominal pain, nausea, vomiting, fever, chills, shortness of breath, headache, or dizziness. He was hospitalized and his diagnostic tests showed an elevated serum glucose of 231 mg/dL (reference range: 65-99 mg/dL), normal ECG, low sodium (sodium 133 mmol/L [reference range: 136-145 mmol/L], and a normal troponin-I troponin- I 23.1 ng/L [reference range: ≤78.5 ng/L]). A head CT showed no acute intracranial findings. A CT of the chest showed a mass within the upper lobe of the left lung. A biopsy was performed and showed moderate to poorly differentiated squamous cell carcinoma and the subject was diagnosed with the AE of moderate squamous cell carcinoma of the lung. On Study Day 94, the subject recovered from the event of syncope and was discharged. The subject permanently discontinued the study drug and study because of the SAE of syncope.

Reviewer comment: Although no other symptoms were reported with the syncopal event and low blood pressure was not documented, the SAE of syncope may represent a case of anaphylaxis given occurrence within minutes of the onset of the infusion.

Intestinal Obstruction and Intestinal Perforation, Colitis, and Hernia

The reader is referred to the [narratives](#) section of the Intestinal Obstruction and Intestinal Perforation section for narratives of serious cases related to Intestinal Obstruction and Perforation, Colitis, and Hernia.

Gastroenteritis

Three SAEs related to Gastroenteritis were identified in 3 subjects in the all-donanemab pool. Preferred terms included gastroenteritis, Crohn's disease, and gastrointestinal infection.

In the three cases related to the topic of gastroenteritis, this reviewer did not establish a role for donanemab. In one SAE of Crohn's disease (verbatim term: worsening of Crohn's disease), this reviewer did not identify a role for donanemab as the event occurred over 200 days after the last donanemab dose (Crohn's disease, I5T-MC-AACI-^{(b) (6)}). In one SAE of

gastrointestinal infection, a role could not be established because of missing information related to the details of hospitalization, such as laboratory tests and treatment received (gastrointestinal infection, I5T-MC-AACI- (b) (6)). In one SAE of gastroenteritis, a role could not be established due to the timing of the event (gastroenteritis, I5T-MC-AACG- (b) (6)). The SAE occurred 26 days after the 10th dose of donanemab and the subject went on to receive an additional 9 doses of donanemab without recurrence of the event.

Gastritis/Duodenitis

Seven SAEs related to gastritis/duodenitis were reported in six subjects in the all-donanemab pool. Preferred terms included vomiting (n=3), erosive gastritis (n=2), duodenitis, and gastritis.

A role for donanemab could not be ruled out in the cases as SAEs of gastritis/duodenitis were reported with higher incidence in the donanemab-treated subjects compared to placebo in the placebo-controlled pool. Outcomes were fatal in two cases. In one of the two cases, the subject reported two episodes of erosive gastritis, occurring 11 days after the 3rd dose and then 28 days later (I5T-MC-AACI- (b) (6)). The subject had underlying gastroesophageal reflux disease as a risk factor for the events. In the second case occurring in a subject with fatal outcome, the subject was suspected to have had an obstructive lesion that had caused the SAEs of gastric obstruction, duodenitis, and pancreatitis (I5T-MC-AACI- (b) (6)). In one case, the subject developed intractable vomiting 23 days after the 6th infusion and was ultimately diagnosed with esophageal dysmotility (I5T-MC-AACI- (b) (6)). In two cases of vomiting, a role could not be established as the events occurred more than 60 days after the last donanemab dose (I5T-MC-AACI- (b) (6) and I5T-MC-AACN- (b) (6)). In the remaining case, the subject had risk factors for the development gastritis, including alcohol and tobacco use (I5T-MC-AACI- (b) (6)).

Acute myocardial infarction

Nine SAEs with preferred term of Acute myocardial infarction were reported in nine subjects.

In the placebo-controlled pool, four SAEs of acute myocardial infarction were reported in donanemab-treated subjects compared to none on placebo (0.4% versus none, respectively).¹²⁰ The imbalance in SAEs of acute myocardial infarction was not explained by an imbalance in preexisting cardiac disease at baseline as donanemab- and placebo-treated subjects had similar incidences (24.4% versus 26.6%, respectively).¹²¹

In one of the cases, the subject also experienced a fatal outcome and is discussed in the Deaths

¹²⁰ Using the analysis method of on drug or within 57 days of the last dose of study drug: I5T-MC-AACI- (b) (6) I5T-MC-AACI- (b) (6) I5T-MC-AACI- (b) (6) and I5T-MC-AACI- (b) (6).

¹²¹ 90Day Safety ADMH dataset with MHSOC = cardiac disorders, and EXISTFL = Y.

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section of this review ([I5T-MC-AACI-](#)(b) (6)). In this case, a role for donanemab in the event could not be ruled out because of the imbalance in SAEs of acute myocardial infarction in the placebo-controlled pool. Other likely contributory factors included pain from Grade IV esophagitis causing elevated blood pressure with an NSTEMI in the setting of hypertensive emergency (blood pressure 212/110 mmHg).

In one case, the event occurred in the setting of elevated blood pressure and other symptoms consistent with an infusion related reaction. The case is summarized above in the Hypersensitivity and Infusion Related Reaction section of the SAEs narratives ([I5T-MC-AACI-](#)(b) (6)).

In the remaining cases, this reviewer did not rule out a role for donanemab. However, this reviewer notes that the cases had underlying risk factors for myocardial infarction, including coronary artery disease ([I5T-MC-AACI-](#)(b) (6) [I5T-MC-AACI-](#)(b) (6) [I5T-MC-AACI-](#)(b) (6) and [I5T-MC-AACI-](#)(b) (6)); carotid artery stenosis and hyperlipidemia ([I5T-MC-AACI-](#)(b) (6)); aortic aneurysm, hypertension, hyperlipidemia ([I5T-MC-AACI-](#)(b) (6)); and hypertension and hyperlipidemia ([I5T-MC-AACI-](#)(b) (6)).

Cardiac Arrest

Three SAEs with the preferred term of Cardiac arrest were reported in three subjects.

This reviewer did not identify a role for donanemab two of the cases, because the event occurred greater than 150 days after the last dose of donanemab ([I5T-MC-AACI-](#)(b) (6) and [I5T-MC-AACI-](#)(b) (6)).

In the third case, a role for the SAE could not be ruled out because of the imbalance of acute myocardial infarction in the placebo-controlled pool ([I5T-MC-AACI-](#)(b) (6)). In this case of cardiac arrest, which also included two separate events of myocardial infarction and one event of ventricular fibrillation (occurring in the setting of myocardial infarction), the subject had a history of coronary artery disease as a risk factor. The event of cardiac arrest occurred 25 days after the 12th dose.

Sinus node dysfunction

Three SAEs with the preferred term of sinus node dysfunction were reported in three subjects in the combined initial submission and resubmission. Verbatim terms for all three events were sick sinus syndrome.

In the placebo-controlled pool, two SAEs of sinus node dysfunction were reported in

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donanemab-treated subjects compared to none on placebo (0.2% versus none, respectively).¹²²

In all three cases, this reviewer did not establish a role for donanemab because of presence of risk factors that were likely contributory to the SAEs of sinus node dysfunction, including history of atrial fibrillation (I5T-MC-AACG- (b) (6)), coronary artery disease, AV block, atrial fibrillation (I5T-MC-AACI- (b) (6)), and history of recurrent syncopal episodes and bradycardia (I5T-MC-AACI- (b) (6)).

AV Block

This reviewer noted four serious cases of atrioventricular block in the all-donanemab pool with preferred term of atrioventricular block complete (n=3) or atrioventricular block.

This reviewer did not establish a role for donanemab in any of the cases. One case occurred more than 6 months after the last dose of donanemab (I5T-MC-AACI- (b) (6)). One case had past medical history of AV block as a risk factor (I5T-MC-AACI- (b) (6)). The remaining two cases had concomitant use with donepezil as a risk factor, which carries a Warnings statement in the packaging insert for heart block (I5T-MC-AACI- (b) (6) and I5T-MC-AACI- (b) (6)). The latter two subjects also had chronic medical conditions as risk factors (I5T-MC-AACI- (b) (6) (b) (6) coronary artery calcifications noted on CT of the chest, I5T-MC-AACI- (b) (6) dyslipidemia).

Hypertension-Related Events

Nine SAEs related to the topic of hypertension were reported in nine subjects. Preferred terms included hypertensive urgency (n=7), hypertension, and hypertensive emergency.

In the placebo-controlled pool, one SAE related to hypertension was reported in a donanemab-treated subject compared to none on placebo (0.1% versus none, respectively).¹²³

This reviewer did not identify a role for donanemab in the event in five cases as the SAE onset was greater than 100 days from the last dose of donanemab (I5T-MC-AACI- (b) (6) I5T-MC-AACI- (b) (6) I5T-MC-AACI- (b) (6) I5T-MC-AACI- (b) (6) I5T-MC-AACI- (b) (6)) or in one case in a subject with past medical history of hypertension and onset of 59 days after the last donanemab dose (I5T-MC-AACI- (b) (6)).

In one case, a role could not be established as the subject had as risk factor a history of hypertension (I5T-MC-AACI- (b) (6)).

¹²² Using the analysis method of on drug or within 57 days of the last dose of study drug.

¹²³ Using the analysis method of on drug or within 57 days of the last dose of study drug.

In the remaining case, with preferred term of hypertensive emergency, this reviewer did not establish a role for donanemab as the subject was reported to have pain from Grade IV esophagitis, which may have been contributory to the SAE of hypertensive emergency (I5T-MC-AACI- (b) (6)). The case also reported an SAE with fatal outcome (preferred term of Dementia Alzheimer's type) and the SAE of acute myocardial infarction. The case is discussed in the Deaths section of this review and in the Acute myocardial infarction SAEs section of this review.

Dehydration

This reviewer identified eight SAEs with preferred term of dehydration, occurring in eight subjects in the all-donanemab pool.

Two of the SAEs had fatal outcome and are discussed further in the Deaths section of this review. In one case, this reviewer did not establish a role for donanemab because of likely contributory factors of dysphagia and placement on palliative care (I5T-MC-AACI- (b) (6)). In the second case, a role for donanemab was unlikely as the SAE occurred 121 days after the last dose of donanemab (I5T-MC-AACI- (b) (6)).

In the remaining six cases, the reviewer did not rule out a role for donanemab given the imbalance with the SAE of dehydration in the placebo-controlled pool. The following table summarizes narratives for these remaining 6 cases.

Table 75. Summary of Remaining 6 Cases of SAEs of Dehydration

USUBJID	Comments
I5T-MC-AACI- (b) (6) PC	66 yo F who also experienced the SAE of syncope Other potential contributory factors: decreased oral intake, receipt of the Covid-19 vaccine 4 days before Occurred 12 days after the 2 nd dose
I5T-MC-AACI- (b) (6) PC	82 yo M Other potential contributory factor: recent travel Occurred 13 days after the 13 th dose
I5T-MC-AACG- (b) (6) PC	71 yo F with syncopal event while at an amusement park. Other potential contributory factor: the subject did not eat on day of the SAE

USUBJID	Comments
I5T-MC-AACG-02168 PC (b) (6)	79 yo F with SAE of dehydration who was seen in the ER the day prior for fall and was also recovering from pneumonia. Other potential contributory factor: concomitant medication included hydrochlorothiazide/triamterene Occurred 26 days after the 7th dose.
I5T-MC-AACI-AP (b) (6)	72 yo F with CKD. Occurred 5 days after 3rd dose
I5T-MC-AACI-AP (b) (6)	79 yo F who developed bradycardia and dehydration. Other potential contributory factor: on therapy with triamterene Occurred 13 days after 3rd dose

AP: all-donanemab pool. F: female. M: male. PC: placebo-controlled pool.

Pneumonia

Including the SAEs in the initial donanemab submission, a total of 31 SAEs with preferred term of Pneumonia (n=25), Covid-19 pneumonia (n=2), aspiration pneumonia (n=2), bacterial pneumonia, and legionella pneumonia were identified, occurring in 29 subjects in the all-donanemab pool.¹²⁴

A role for donanemab in the SAEs of pneumonia could not be ruled out as pneumonia was reported with higher incidence in the donanemab arm compared to placebo in the placebo-controlled pool.

All of the cases had at least age or dementia as risk factor for pneumonia. Twenty-eight of the 31 subjects were at least 70 years of age or older. Twenty-four of the 31 subjects had dementia upon screening (based on MMSE score).

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Three of the 31SAEs of pneumonia had fatal outcomes and are discussed in the Deaths section of this review ([I5T-MC-AACG-\[REDACTED\]](#)^{(b) (6)}, [I5T-MC-AACI-\[REDACTED\]](#)^{(b) (6)} and [I5T-MC-AACI-\[REDACTED\]](#)^{(b) (6)}). (This reviewer notes an additional two cases related to the topic of pneumonia are included in the [Deaths section](#) of this review that had preferred terms of acute respiratory failure and Covid-19).¹²⁵

Covid-19

This reviewer identified 19 SAEs with preferred term of Covid-19, occurring in 18 subjects.¹²⁶

This reviewer did not rule out a role for donanemab in the SAEs of Covid-19 as Covid-19 and pneumonia were SAEs reported with higher incidence in donanemab-treated subjects compared to placebo in the placebo-controlled pool. This reviewer notes that the subjects developed Covid-19 after they had received between one and 15 doses of donanemab.

One of the cases had a fatal outcome and is summarized in the Deaths section of this review (15T-MC-AACI- (b) (6)).

Pulmonary Embolism

This reviewer identified ten SAEs with the preferred term Pulmonary embolism, occurring in ten subjects in the all-donanemab pool.¹²⁷

In two cases of pulmonary embolism, this reviewer did not establish a role given the time between the onset of the AE and the last dose. In one case, the event occurred more than 11 months after the last donanemab dose (15T-MC-AACG- (b) (6)). In a second case, a case with fatal outcome, the SAE occurred 74 days after the last dose of donanemab ([15T-MC-AACI- \(b\) \(6\)](#)).

In the remaining eight cases, a role for donanemab could not be ruled out, given that

125 Additional two SAEs with fatal outcome related to the topic of pneumonia: I5T-MC-AACI- (b) (6) and I5T-MC-AACI- (b) (6)

126 Participants with SAEs of Covid-19: 15T-MC-AACT- (b) (6) 15T-MC-AACT- (b) (6) 15T-MC-AACT- (b) (6)
15T-MC-AACT- (b) (6) 15T-MC-AACT- (b) (6) 15T-MC-AACT- (b) (6) 15T-MC-AACT- (b) (6) 15T-MC-
AACT- (b) (6), 15T-MC-AACT- (b) (6) 15T-MC-AACT- (b) (6) 15T-MC-AACT- (b) (6) 15T-MC-AACT- (b) (6)
(b) (6) 15T-MC-AACT- (b) (6), 15T-MC-AACT- (b) (6) 15T-MC-AACT- (b) (6) 15T-MC-AACT- (b) (6) 15T-
MC-AACT (b) (6) and 15T-MC-AACT- (b) (6)

127 The following donanemab-treated participants reported pulmonary embolisms while on study drug or within 57 days of the last dose in the placebo-controlled pool: 15T-MC-AACG- (b) (6) 15T-MC-AACG- (b) (6) 15T-MC-AACI- (b) (6), 15T-MC-AACI- (b) (6), and 15T-MC-AACI- (b) (6). These same participants were also participants with pulmonary embolism who made up the donanemab arm in the placebo-controlled pool using the treatment period + 57 days analysis method.

pulmonary embolism was reported with higher incidence in donanemab-treated subjects compared to placebo in the placebo-controlled pool. One case was fatal and is discussed further in the Deaths section of this review ([I5T-MC-AACI-\[REDACTED\]](#)^{(b) (6)}). In three cases, this reviewer considered the subjects to be low risk for pulmonary embolism, with one subject having no identifiable risk factors (I5T-MC-AACG-[REDACTED]^{(b) (6)} with pulmonary embolism occurring after 13th donanemab infusion) and the remaining two subjects having history of non-metastatic breast cancer diagnosed over 25 years before (I5T-MC-AACI-[REDACTED]^{(b) (6)}) and testosterone therapy for greater than 10 years and concurrent acute deep vein thrombosis in lower leg (I5T-MC-AACI-[REDACTED]^{(b) (6)}) as risk factors.¹²⁸ Of note, testosterone has a Warning in the prescribing information regarding venous thromboembolism including pulmonary embolism, although Martinez et al report that the risk is greatest up to 6 months of use.¹⁴¹ In the four remaining cases, the subject's had risk factors for pulmonary embolism, including atrial fibrillation (I5T-MC-AACI-[REDACTED]^{(b) (6)}), obstructive sleep apnea (I5T-MC-AACI-[REDACTED]^{(b) (6)}), and hospitalization and recent surgery (I5T-MC-AACN-[REDACTED]^{(b) (6)} and I5T-MC-AACI-[REDACTED]^{(b) (6)}).

Pancreatitis

This reviewer identified three SAEs related to the topic of pancreatitis occurring in 3 subjects in the all-donanemab pool. Preferred terms were acute pancreatitis (n=2) and pancreatitis.

This reviewer did not identify a role for donanemab in the cases. One case occurred in a subject who had a fatal outcome from the SAE of respiratory arrest ([I5T-MC-AACI-](#)(b) (6)). In this case, the death certificate indicated that death was possibly secondary to an obstructive lesion causing pancreatitis, duodenitis, and esophagitis. The case is discussed further in the Deaths section of this review. The remaining two cases had potential risk factors, including a diagnosis of microscopic colitis (diagnosed 8 days before), which has been associated with acute pancreatitis,¹²⁹ and past medical history of pancreas divisum ([I5T-MC-AACI-](#)(b) (6)) and a history of chronic pancreatitis ([I5T-MC-AACI-](#)(b) (6)).

Falls

In the all-donanemab pool, this reviewer identified 18 SAEs with the preferred term of Fall, occurring in 17 subjects.¹³⁰

¹²⁸ Martinez C, Suissa S, Riethbrock S. et al. Testosterone treatment and risk of venous thromboembolism: population based case-control study. *BMJ* 2016;355:i5968 oi: <https://doi.org/10.1136/bmj.i5968>

¹²⁹ Bergman D, Roelstraete B, Olén O, et al. Microscopic Colitis and Risk of Incident Acute Pancreatitis: A Nationwide Population-Based Matched Cohort Study. *Am J Gastroenterol* 2023;118:2041–2051. <https://doi.org/10.14309/ajg.0000000000002318>

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In the 17 subjects with SAEs of falls, this reviewer notes that the number of doses subjects had received prior to the first SAE of fall ranged from 1 to 15 doses.

In three cases, this reviewer did not identify a role for donanemab as the events occurred greater than 50 days after the last dose of donanemab (I5T-MC-AACI- (b) (6) I5T-MC-AACI- (b) (6) and I5T-MC-AACI- (b) (6)).

In the remaining 14 subjects, the SAEs occurred between 3 and 39 days after the last dose of donanemab.

In one case, the reviewer noted that a potential contributory factor to the SAE of fall may have been ARIA-E. The case is summarized in the cerebral infarction section above ([I5T-MC-AACI- \(b\) \(6\)](#)).

In the remaining 13 subjects with SAEs of fall, this reviewer did not rule out a role for donanemab given that fall was reported with higher incidence in the donanemab arm compared to placebo in the placebo-controlled pool. However, this reviewer notes that the 13 subjects had underlying risk factors for fall, including medical history (peripheral neuropathy, lumbar spinal stenosis, BPPV/I5T-MC-AACG- (b) (6) bilateral hip replacement and right knee replacement/I5T-MC-AACI- (b) (6) bilateral foot neuropathy/I5T-MC-AACI- (b) (6) bilateral knee replacements/I5T-MC-AACI- (b) (6) history of intermittent lightheadedness from poor oral intake/ I5T-MC-AACI- (b) (6) and history of recent fall prior to initiating therapy with donanemab/ I5T-MC-AACI- (b) (6)), concurrent event potentially contributing to the event of fall (fall while playing softball/I5T-MC-AACI- (b) (6) poor fluid intake, urinary tract infection, Klebsiella pneumonia, Covid infection/I5T-MC-AACI- (b) (6) fall from ladder/I5T-MC-AACI- (b) (6) fall after playing with pet cat and fall after recent diagnosis of rib fracture/I5T-MC-AACN- (b) (6) fall while exiting a cab with loose shoes/I5T-MC-AACI- (b) (6) fall while pulling on a still-locked car door handle/I5T-MC-AACI- (b) (6) or concurrent event of syncope occurring in the setting of low blood pressure while on a medication for high blood pressure (I5T-MC-AACI- (b) (6))).

The reader is referred to the [Deaths section](#) of this review for a review of SAEs with fatal outcome related to the topic of Trauma.

Acute Kidney Injury

This reviewer identified nine SAEs with preferred term acute kidney injury, occurring in eight subjects.

MC-AACI- (b) (6) I5T-MC-AACI- (b) (6) I5T-MC-AACI- (b) (6) I5T-MC-AACI- (b) (6) I5T-MC-AACI- (b) (6) and I5T-MC-AACN- (b) (6)

This reviewer did not establish a role for donanemab in five cases because of concurrent events that were potentially contributory. Concurrent events included pneumoperitoneum (I5T-MC-AACI- (b) (6)), dehydration (I5T-MC-AACI- (b) (6)), Covid-19 infection (I5T-MC-AACI- (b) (6)), myocardial ischemia (I5T-MC-AACI- (b) (6)) and gastric outlet obstruction (I5T-MC-AACI- (b) (6)).

In the remaining three cases, this reviewer did not establish a role for donanemab in the SAEs. In one case, the subject had a history of chronic kidney disease Stage 3 as past medical history, which was a likely contributory factor (I5T-MC-AACI- (b) (6)). Another subject had concomitant medication use with meloxicam as a potential risk factor (I5T-MC-AACI- (b) (6)). In the remaining case, the subject developed acute renal failure (creatinine of 1.4 mg/dL [reference range of 0.6 – 1.3] in the setting of syncopal event and suspected dehydration 18 days after the 6th dose and again in the setting of dehydration 4 days after the 16th dose (I5T-MC-AACI- (b) (6)). The subject recovered and no action was taken with the drug.

Non-cardiac Chest Pain

Fourteen SAEs of non-cardiac chest pain, occurring in 14 subjects, were reported in the all-donanemab pool. Preferred terms included chest pain (n=7), non-cardiac chest pain (n=4), musculoskeletal chest pain (n=2), and chest discomfort.

This reviewer did not establish a role for donanemab in three cases as the events occurred more than 80 days after the last donanemab dose (I5T-MC-AACI- (b) (6) I5T-MC-AACI- (b) (6) and I5T-MC-AACI- (b) (6)).

A role could not be established in 3 subjects because of underlying risk factors, including missed dosages of omeprazole (I5T-MC-AACI- (b) (6)), concomitant prednisone use (I5T-MC-AACI- (b) (6)), and fall causing musculoskeletal pain (I5T-MC-AACI- (b) (6)).

In the remaining 8 cases, this reviewer did not identify a role for donanemab in the cases.¹³¹ SAEs occurred after between 4 and 22 doses. Time from the last donanemab dose ranged between 6 and 49 days. One of the cases may have been caused by esophageal stricture (I5T-MC-AACI- (b) (6)). In six of the seven remaining cases, the subjects received at least one additional dose of donanemab and none of these subjects had recurrence of chest pain.¹³²

¹³¹ I5T-MC-AACI- (b) (6) I5T-MC-AACI- (b) (6) I5T-MC-AACI- (b) (6) I5T-MC-AACI- (b) (6) I5T-MC-AACI- (b) (6) and I5T-MC-AACI- (b) (6)

¹³² I5T-MC-AACI- (b) (6) I5T-MC-AACI- (b) (6) I5T-MC-AACI- (b) (6) I5T-MC-AACI- (b) (6) I5T-MC-AACI- (b) (6) and I5T-MC-AACI- (b) (6)

Hyperglycemic Events

In the all-donanemab pool, three SAEs related to diabetic ketoacidosis were reported in three subjects (preferred terms of Diabetic ketoacidosis (n=2) and Diabetic ketosis). One additional case related to the event of hyperglycemia was reported during the 90-Day Safety Update and included the preferred term of seizure.

In the placebo-controlled pool, there were no serious events in donanemab-treated subjects compared to two serious events in placebo-treated subjects (none versus 0.2%, respectively).¹³³

A role for donanemab in the cases could not be ruled out as TEAEs related to hyperglycemia were reported with higher incidence in donanemab-treated subjects in the placebo-controlled pool (1.6% versus 0.8%, respectively).¹³⁴ One case had as risk factor concomitant medication use with empagliflozin, which has been associated with ketosis (I5T-MC-AACI- (b) (6)).¹³⁵ In the case of seizure included in the 90-Day Safety update, the seizure occurred in a subject who had developed diabetic ketoacidosis (I5T-MC-AACI- (b) (6)). The SAE of seizure occurred 15 days after the first dose. The subject was on oral medications (glimepiride, metformin, and pioglitazone) prior to developing diabetic ketoacidosis. In the remaining two subjects, the serious AEs occurred after the 5th and 8th dose of donanemab and the subjects received 3 and 6 more additional doses of donanemab without recurrence of events (I5T-MC-AACG- (b) (6) and I5T-MC-AACI- (b) (6) respectively).

Hyponatremic Events

Six SAEs with preferred term of hyponatremia were reported in six subjects.

In the placebo-controlled pool, two donanemab-subjects reported SAEs of hyponatremia compared to one on placebo (0.2% versus 0.1%, respectively).¹³⁶

In two cases, a role for donanemab was unlikely as the event occurred greater than 100 days after the last dose of donanemab (I5T-MC-AACI- (b) (6) and I5T-MC-AACI- (b) (6)).

In the remaining four cases, a role for donanemab in the SAEs of hyponatremia could not be ruled out as TEAEs of hyponatremia were reported with higher incidence in donanemab-treated

¹³³ Placebo-treated participants with SAEs related to hyperglycemia: I5T-MC-AACG-145-02293/Diabetes mellitus and I5T-MC-AACI- (b) (6) /Diabetic Ketoacidosis.

¹³⁴ Donanemab-treated participants with SAEs related to hyperglycemia: I5T-MC-AACI- (b) (6) I5T-MC-AACI- (b) (6) I5T-MC-AACI- (b) (6) and I5T-MC-AACG- (b) (6)

¹³⁵ Jardiance. Labeling-Prescribing Information. Drugs@fda.gov. Action date September 12, 2023. Accessed September 15, 2023.

¹³⁶ Using the analysis method of on drug or within 57 days of the last dose of study drug.

Clinical Review
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BLA 761248
Kisunla/donanemab

subjects in the placebo-controlled period of AACI (1.5% versus 0.5%, respectively).¹³⁷ This reviewer notes that two of the four cases had potential risk factors of urinary tract pathology which may have been contributory to the events (urinary retention in the setting of stage IV cervical cancer, I5T-MC-AACI- (b) (6) and urinary tract infection I5T-MC-AACI- (b) (6)).¹³⁸

Suicide-Related Events

This reviewer identified three SAEs related to the topic of suicide-related events, occurring in three subjects (preferred terms: completed suicide [n=2] and suicide attempt).

In the placebo-controlled pool, there was not an imbalance in suicide-related SAEs (0.2%, based on two cases in each arm).¹³⁹

Two of the cases had fatal outcome and are discussed in the Deaths section of this review (I5T-MC-AACI- (b) (6) and I5T-MC-AACI- (b) (6)). The reviewer did not identify a role for donanemab in the events as the subject's had past medical history as a potential contributory factor.

In the remaining case, this reviewer did not identify a role for donanemab in a subject who reported the SAE of suicide attempt as the event occurred more than 150 days after the last donanemab dose (I5T-MC-AACI- (b) (6)).

Other SAEs

This reviewer did not identify a role for donanemab in a subject who develop the SAE of priapism as the event occurred one day following use of papaverine phentolamine for treatment of erectile dysfunction (I5T-MC-AACI- (b) (6)).

This reviewer did not identify a role for donanemab in a subject who reported the SAE of road traffic accident (I5T-MC-AACI- (b) (6)), which occurred 2 days after the 19th dose of donanemab.

This reviewer identified three cases related to the topic of encephalopathy, occurring in three subjects (preferred terms: metabolic encephalopathy [n=2] and encephalopathy). The reviewer did not identify a role for donanemab in the cases. In one case with fatal outcome, the SAE occurred > 100 days after the last donanemab dose (I5T-MC-AACG- (b) (6)). The case is

¹³⁷ Donanemab-treated participants with SAEs of hyponatremia: I5T-MC-AACI- (b) (6) I5T-MC-AACI- (b) (6) I5T-MC-AACI- (b) (6) and I5T-MC-AACI- (b) (6)

¹³⁸ Parikh J, Dhareshwar S, Nayak-Rao S, et al. Hyponatremia secondary to acute urinary retention. Saudi journal of kidney diseases and transplantation 2017; 28(2): 392-395. DOI: 10.4103/1319-2442.202768; PMID: 28352026

¹³⁹ Using the analysis method of on drug or within 57 days of the last dose of study drug.

discussed further in the Deaths section of this review. In the second case, concurrent events of orthostatic hypotension and elevated creatinine were likely contributory (I5T-MC-AACI- (b) (6)). In the remaining case, this reviewer did not establish a role for donanemab due to likely contributory factors of urinary tract infection, indwelling foley catheter, benign prostatic hypertrophy, and chronic kidney disease (I5T-MC-AACI- (b) (6)).

One subject had the SAE of Chronic kidney disease reported 27 days after the 7th dose of donanemab (I5T-AACI- (b) (6)). This reviewer did not identify a role for donanemab in the event as the subject had chronic kidney disease as an underlying risk factor for the event.

One subject experienced the SAE of visual hallucinations 14 days after the 13th dose (I5T-MC-AACI- (b) (6)). In this case, this reviewer did not establish a role for donanemab in the event. An MRI within 10 days of the event did not show any change from a previous MRI (no evidence of ARIA-E, new microhemorrhages, macrohemorrhage or superficial siderosis).

13.11. Study Withdrawal

In the placebo-controlled period of AACI, 26.5% (226/853) of donanemab-treated subjects and 19.9% (174/874) of placebo-treated subjects withdrew from the study. The following table shows study disposition in the placebo-controlled period of AACI after the 90-Day Safety Update.¹⁴⁰ Similar findings were observed in the placebo-controlled pool.

Table 76. Study Disposition for the Placebo-controlled Period of AACI after the 90-Day Safety Update

Preferred Term	Donanemab N=853 n (%)	Placebo N=874 n (%)
Completed	38 (4.5)	24 (2.7)
Completed and Continuing to LTE	587 (68.8)	674 (77.1)
Ongoing	2 (0.2)	2 (0.2)
Withdrew from Study	226 (26.5)	174 (19.9)
Adverse event	50 (5.9)	22 (2.5)
Death	16 (1.9)	10 (1.1)
Lost to follow-up	11 (1.3)	11 (1.3)
Physician decision	16 (1.9)	9 (1)

¹⁴⁰At the time of the 90-Day Safety Update four subjects from the placebo-controlled period of AACI continued to be ongoing in the study. Three of the four were also noted to be continuing to receive treatment. In a submission dated October 19, 2023, the Applicant noted that these participants had either not had treatment status updated in the corresponding dataset or had discontinued from the study in the week following the 90-Day Safety data cutoff point.

Preferred Term	Donanemab N=853 n (%)	Placebo N=874 n (%)
Progressive disease	4 (0.5)	7 (0.8)
Withdrawal by subject	108 (12.7)	95 (10.9)
Withdrawal due to caregiver circumstances	21 (2.5)	20 (2.3)

The reviewer created this table: For Completed, Completed and Continuing to LTE, and Discontinued categories; 90-Day Safety Update IDB ADDS, APERIOD = 1, PARAM = Study Disposition. For Ongoing category: 90 Day Safety Update IDB where ADSL with PCSAFL = Y, subset for columns USUBJID and TR01PG, and joined with ADDS, APERIOD = 1, Param = Study Disposition, selected on USUBJID of ADDS = “ “.

Most subjects who discontinued treatment also withdrew from the study in both donanemab and placebo arms of the placebo-controlled period of AACI (85.9% and 96%, respectively).

Vital status remained unknown for 22 subjects from the AACI placebo-controlled period that were lost to follow up (11 in placebo and 11 in donanemab). Among the donanemab-treated subjects, none had an ongoing SAE, none had an ongoing ARIA-E event, and among the 5 subjects with an ongoing ARIA-H event, none had macrohemorrhage, were serious, or were symptomatic.¹⁴¹

In the placebo-controlled period of Study AACI, infusion related reaction and ARIA-E were the most frequent adverse events reported to lead to study withdrawal. Similar findings were observed in the placebo-controlled pool.

Table 77. TEAEs Reported to Lead to Study Withdrawal by Preferred Term with Incidence of at Least 0.2% Higher in the Donanemab Arm Compared to Placebo in the Placebo-Controlled Period of AACI

Preferred Terms	Donanemab (N = 853)	Placebo (N = 874)
Total Subjects with any AE Reported to Lead to Study Withdrawal	67 (7.9%)	29 (3.3%)
Infusion related reaction	19 (2.2%)	0 (0.0%)
Amyloid related imaging abnormality-edema/effusion	10 (1.2%)	2 (0.2%)
Amyloid related imaging abnormality-microhemorrhages and hemosiderin deposits	5 (0.6%)	0 (0.0%)
Agitation	3 (0.4%)	0 (0.0%)
Death	2 (0.2%)	0 (0.0%)
Delirium	2 (0.2%)	0 (0.0%)

¹⁴¹ February 29, 2024, response to an information request.

Preferred Terms	Donanemab (N = 853)	Placebo (N = 874)
Hypersensitivity	2 (0.2%)	0 (0.0%)
Plasma cell myeloma	2 (0.2%)	0 (0.0%)
Pneumonia	2 (0.2%)	0 (0.0%)
Pulmonary embolism	2 (0.2%)	0 (0.0%)

This table was created by Senior Clinical Analyst Dr. Rui Li using the 90-Day Safety Update ADAE dataset.

A higher incidence of donanemab-treated subjects withdrew from the study due to adverse events compared to placebo in the placebo-controlled pool (7.1% versus 2.8%, respectively).¹⁴² The following table shows study disposition events for the placebo-controlled pool.

Table 78. Study Disposition for the Placebo-controlled Pool after the 90-Day Safety Update

Preferred Term	Donanemab N=984 n (%)	Placebo N=999 n (%)
Completed	132 (13.4)	117 (11.7)
Completed and Continuing to LTE	587 (59.7)	674 (67.5)
Ongoing	2 (0.2)	2 (0.2)
Withdrew	263 (26.7)	206 (20.6)
Adverse event	70 (7.1)	28 (2.8)
Death	17 (1.7)	12 (1.2)
Lost to follow-up	11 (1.1)	11 (1.1)
Other	3 (0.3)	8 (0.8)
Physician decision	16 (1.6)	10 (1)
Progressive disease	4 (0.4)	7 (0.7)
Protocol deviation	1 (0.1)	1 (0.1)
Withdrawal by subject	120 (12.2)	107 (10.7)
Withdrawal due to caregiver circumstances	21 (2.1)	22 (2.2)

The reviewer created this table: For Completed, Completed and Continuing to LTE, and Discontinued categories; 90-Day Safety Update IDB ADDS, APERIOD = 1, PARAM = Study Disposition. For Ongoing category: 90 Day Safety Update IDB where ADSL with PCSAFL = Y, subset for columns USUBJID and TR01PG, and joined with ADDS, APERIOD = 1, Param = Study Disposition, selected on USUBJID of ADDS = “ ”.

A lower incidence of subjects reported adverse events leading to study withdrawal in the all-donanemab pool compared to the AACI placebo-controlled period (5.8% versus 7.9%, respectively). The lower incidence observed in the all-donanemab pool maybe due to selection

¹⁴² Incidence of AEs reported to lead to discontinuation based on disposition dataset (ADDS).

bias as subjects who previously received donanemab and did not experience an adverse event maybe more likely to continue to receive study drug. Similar to the AACI placebo-controlled period, infusion related reaction and ARIA-E were among the most frequently reported TEAEs leading to study withdrawal (occurring in 1.7% and 0.9% of subjects, respectively).

The following table showing the most frequent TEAEs reported to lead to study withdrawal by preferred term in the all-donanemab pool.

Table 79. TEAEs Reported to Lead to Study Withdrawal by Preferred Term with Incidence of at Least 0.3% in the All-Donanemab Pool

Preferred Terms	Donanemab (N =2802)
Total Subjects with any Adverse Events	162 (5.8%)
Infusion related reaction	47 (1.7%)
Amyloid related imaging abnormality-oedema/effusion	24 (0.9%)

This table was created by Senior Clinical Analyst Dr. Rui Li using the 90-Day Safety Update ADAE dataset.

13.12. Treatment Discontinuation

The following table shows treatment disposition for the placebo-controlled period of AACI after the 90-Day Safety Update. Similar findings of percentage of subjects discontinuing treatment were observed for the placebo-controlled pool.

Table 80. Treatment Disposition for the Placebo-controlled Period of AACI after the 90-Day Safety Update.

Preferred Term	Donanemab N=853 n (%)	Placebo N=874 n (%)
Completed	27 (3.2)	25 (2.9)
Completed and Continuing to LTE	569 (66.7)	672 (76.9)
Continuing Treatment	2 (0.2)	1 (0.1)
Discontinued	255 (29.9)	176 (20.1)
Adverse event	98 (11.5)	27 (3.1)
Death	15 (1.8)	9 (1)
Discontinued	3 (0.4)	1 (0.1)
Lost to follow-up	9 (1.1)	10 (1.1)
Physician decision	18 (2.1)	10 (1.1)

Preferred Term	Donanemab N=853 n (%)	Placebo N=874 n (%)
Progressive disease	4 (0.5)	7 (0.8)
Withdrawal by subject	92 (10.8)	94 (10.8)
Withdrawal due to caregiver circumstances	16 (1.9)	18 (2.1)

The reviewer created this table: For Completed, Completed and Continuing to LTE, and Discontinued categories; 90-Day Safety Update IDB ADDS, APERIOD = 1, PARAM = Treatment Disposition, STUDYID = AACI. For Continued Treatment category: 90 Day Safety Update IDB where ADSL with PCSAFL = Y, subset for columns USUBJID and TR01PG, and joined with ADDS, APERIOD = 1, Param = Treatment Disposition, selected on USUBJID of ADDS = “ “.

Similar to the placebo-controlled period of AACI, adverse events reported to lead to treatment discontinuation in the placebo controlled pool were reported with higher incidence in the donanemab arm compared to placebo (15.1% versus 4.3%, respectively). Infusion related reaction and ARIA-E were the most frequent adverse events reported to lead to treatment discontinuation in the placebo-controlled pool.

Infusion related reaction and ARIA-E were also the most frequent adverse events reported to lead to treatment discontinuation in the all-donanemab pool. The following table showing the most frequent TEAEs reported to lead to treatment discontinuation by preferred term in the all-donanemab pool.

Table 81. TEAEs Reported to Lead to Treatment Discontinuation by Preferred Term with Incidence of at Least 0.3% in the All-Donanemab Pool

Preferred Terms	Donanemab (N =2802)
Total Subjects with any Adverse Events Reported to Lead to Treatment Discontinuation	289 (10.3%)
Infusion related reaction	81 (2.9%)
Amyloid related imaging abnormality-oedema/effusion	56 (2.0%)
Amyloid related imaging abnormality-microhemorrhages and hemosiderin deposits	25 (0.9%)
Superficial siderosis of central nervous system	12 (0.4%)
Anaphylactic reaction	9 (0.3%)
Hypersensitivity	9 (0.3%)

This table was created by Senior Clinical Analyst Dr. Rui Li using the 90-Day Safety Update ADAE dataset.

13.13. Narratives of Study Withdrawal and Treatment Discontinuation

This reviewer identified adverse events of agitation and delirium as topics of interest based on adverse events reported to lead to study withdrawal or treatment discontinuation in donanemab-treated subjects in the placebo-controlled pool.

Three AEs of agitation were reported to lead to study withdrawal and treatment discontinuation in three subjects in the all-donanemab pool. For two cases, this reviewer did not rule out a role for donanemab in the events. One case, which involved hospitalization for psychotic agitation, occurred 19 days after the first dose in a subject with past medical history of depression and anxiety (I5T-MC-AACI- (b) (6)). The second case occurred 7 days after the first dose and was reported to be mild in severity (I5T-MC-AACI- (b) (6)). In the third case, this reviewer did not identify a role for donanemab. The event occurred 6 days after the 14th dose and the subject was reported to also have recurrent urinary tract infections (I5T-MC-AACI- (b) (6)).

Three events of delirium were reported to lead to study withdrawal in two subjects in the all-donanemab pool. One case, which reported two events of delirium, appeared secondary to hyponatremia, and is discussed in the Deaths section of this review (I5T-MC-AACI- (b) (6)). This reviewer did not establish a role for donanemab in the second case of delirium, as the AE developed several days prior to a diagnosis of Covid-19 infection, which may have been a predisposing factor (I5T-MC-AACI- (b) (6)).

13.14. TEAEs in the Placebo-controlled Pool

The following table shows TEAEs by preferred term with incidence of at least 5% in the donanemab arm and at least 2% greater than placebo in the pooled placebo-controlled pool.

Table 82. TEAEs by Preferred Term with Reported in at least 5% and at least 2% higher in the Donanemab Arm Compared to Placebo for Pooled Placebo-Controlled Studies.

Preferred Term	Donanemab N=984 n (%)	Placebo N=999 n (%)
Total Subjects with any TEAE	877 (89.1)	828 (82.9)
Amyloid related imaging abnormality-edema/effusion ^a	236 (24.0)	18 (1.8)
Amyloid related imaging abnormality-microhemorrhages and hemosiderin deposits ^a	243 (24.7)	105 (10.5)
Superficial siderosis of central nervous system ^a	147 (14.9)	26 (2.6)
Infusion related reaction	84 (8.5)	4 (0.4)
Headache ^b	125 (12.7)	101 (10.1)

This reviewer created this table using the 90-Day Safety IDB ADAE dataset, TEPCLDLFL, APERIODC = First Treatment

Period, STUDYID = AACI.

^aEvents related to ARIA are based on the ARIA events reported in the MRI dataset.

^bThe term headache does not include headache associated with ARIA.

The following table show TEAEs by EMQ and FMQ groupings with incidence of at least 5% in the donanemab arm and at least 2% greater than placebo in the pooled placebo-controlled pool.

Table 83. TEAEs by Preferred Term within EMQ and FMQ Groupings with Incidence of at least 5% and at least 2% higher in the Donanemab Arm Compared to Placebo for Pooled Placebo-Controlled Studies

EMQ and FMQ Groupings	DON N=984 n (%)	PBO N=999 n (%)
Allergic reaction, hypersensitivity	106 (10.8)	15 (1.5)
Infusion Related Reaction	84 (8.5)	4 (0.4)
Hypersensitivity	10 (1)	3 (0.3)
Urticaria	4 (0.4)	1 (0.1)
Anaphylactic Reaction	3 (0.3)	0
Dermatitis Allergic	2 (0.2)	1 (0.1)
Drug Eruption	1 (0.1)	0
Face Oedema	2 (0.2)	1 (0.1)
Lip Swelling	1 (0.1)	0
Angioedema	2 (0.2)	2 (0.2)
Dermatitis Atopic	0	1 (0.1)
Pharyngeal Swelling	0	1 (0.1)
Swelling Face	0	1 (0.1)
Headache FDA N	134 (13.6)	105 (10.5)
Headache	125 (12.7)	101 (10.1)
Post-Traumatic Headache	3 (0.3)	1 (0.1)
Drug Withdrawal Headache	1 (0.1)	0
Occipital Neuralgia	1 (0.1)	0
Procedural Headache	1 (0.1)	0
Sinus Headache	1 (0.1)	0
Tension Headache	1 (0.1)	0
Migraine	3 (0.3)	2 (0.2)
Cluster Headache	0	1 (0.1)

The reviewer created this table using the 90-Day Safety Update IDB ADAE dataset, TEPCDLFL = Y, APERIODC = first treatment period.

The following table show TEAEs by EMQ and FMQ groupings with incidence of at least 5% in the

all-donanemab pool.

Table 84. TEAEs by EMQ and FMQ Groupings with Incidence of at Least 5% in the All-Donanemab Pool at the 90-Day Safety Update¹

EMQ and FMQ Groupings	Donanemab N=2802 n (%)
Infection	562 (20.1)
Urinary tract infection	135 (4.8)
Upper respiratory tract infection	88 (3.1)
Nasopharyngitis	68 (2.4)
Bronchitis	44 (1.6)
Sinusitis	39 (1.4)
Pneumonia	36 (1.3)
Fall, Dizziness, Balance Disorder	433 (15.5)
Fall	291 (10.4)
Dizziness	136 (4.9)
Balance disorder	29 (1)
Headache Fda N	328 (11.7)
Headache	298 (10.6)
Allergic Reaction, Hypersensitivity	286 (10.2)
Infusion related reaction	234 (8.4)
Hemorrhage Fda N	257 (9.2)
Contusion	67 (2.4)
Cerebral microhemorrhage	59 (2.1)
Upper Respiratory Infection, Cold, Rhinitis, Flu-like Illness	220 (7.9)
Upper respiratory tract infection	88 (3.1)
Nasopharyngitis	68 (2.4)
Sinusitis	39 (1.4)
Bleeding	170 (6.1)
Cerebral microhemorrhage	59 (2.1)
Arthralgia, Arthritis, Arthrosis	155 (5.5)
Arthralgia	105 (3.7)
Osteoarthritis	28 (1)
Urinary tract infection	147 (5.2)
Urinary tract infection	135 (4.8)
Dyspepsia, nausea, vomiting, indigestion, epigastric pain, gastritis, duodenitis	142 (5.1)

EMQ and FMQ Groupings	Donanemab N=2802 n (%)
Nausea	90 (3.2)
Vomiting	58 (2.1)

This reviewer created this table using the 90Day Safety IDB ADAE dataset, TELYLDFL.

¹Preferred terms contributing to the groupings with incidence of at least 1% were included in the table above.

13.15. Shift Tables for Additional Laboratory Parameters for the Placebo-controlled Pool

The following section contains information from shift tables from the placebo-controlled pool for the following laboratory parameters: glucose, creatine kinase, leukocytes, lymphocytes, and neutrophils.

Glucose

Similar incidences of glucose shift to high and low were observed in the donanemab and placebo arms in the placebo-controlled pool (difference no greater than 0.3%). Similar incidences of glucose shifts to higher CTCAE grades were observed in the donanemab and placebo arms in the placebo-controlled pool (difference no greater than 4%).

Creatine Kinase

Similar incidences of creatine kinase shift to high and low were observed in the donanemab and placebo arms in the placebo-controlled pool (difference no greater than 1%). A similar incidence of donanemab- and placebo-treated subjects had shifts to higher CTCAE grades of increased creatine kinase (difference no greater than 3%).

Leukocytes

A higher incidence of donanemab-treated subjects had shifts to high or low leukocytes compared to placebo in the placebo-controlled pool; however, the differences between the arms were less than 2%. A similar incidence of donanemab- and placebo-treated subjects had shifts to higher CTCAE grades of decreased leukocytes (difference no greater than 2%).

Lymphocytes

Similar incidences of lymphocytes shift to high and low were observed in the donanemab and placebo arms in the placebo-controlled pool (difference no greater than 1%). A similar incidence of donanemab- and placebo-treated subjects had shifts to higher CTCAE grades of increased lymphocytes (difference no greater than 1%). A similar incidence of donanemab- and

placebo-treated subjects had shifts to higher CTCAE grades of decreased lymphocytes (difference no greater than 3%).

Neutrophils

Similar incidences of neutrophils shift to high and low were observed in the donanemab and placebo arms in the placebo-controlled pool (difference no greater than 1%). A similar incidence of donanemab- and placebo-treated subjects had shifts to higher CTCAE grades of decreased neutrophils (difference no greater than 2%).

13.16. Denominators for ECG collections

The following table shows the number of subjects contributing to ECG collections by week number in the placebo-controlled pool using mean heart rate as an ECG parameter.

Table 85. Number of Subjects Contributing to ECG collection by Visits in the Placebo-Controlled Pool

Week #	Donanemab N=981 ¹	Placebo N=998 ¹
24	817	872
52	723	773
76	692	753

This table was created by this reviewer using analyses provided by Senior Clinical Analyst Dr. Rui Li.

¹Number of subjects with ECGs at baseline.

The following table shows the number of subjects contributing to ECG collections by week number in the all-donanemab pool using mean heart rate as an ECG parameter.

Table 86. Number of Subjects Contributing to ECG collection by Visits in the All-Donanemab Pool

Visit #	Donanemab N=2725 ¹
24	900
52	755
76	699

This table was created by this reviewer using analyses provided by Senior Clinical Analyst Dr. Rui Li.

¹Number of subjects with ECGs at baseline.

13.17. Immunogenicity Data Collection

The immunogenicity of donanemab was evaluated using an anti-drug antibody (ADA) assay and a neutralizing antibody assay. Among Phase 2 and 3 studies, immunogenicity data was collected in Studies AACG, AACI, and AACH. In Study AACI (placebo-controlled and long-term extension period), ADA samples were collected preinfusion on Weeks 0, 4, 8, 12, 16, 24, 36, 52, 76, 90, 102, 130, 154, the early discontinuation visit, and every 12 weeks beginning after their last dose of investigational product for up to approximately one year after the last dose if the subject had TE ADA positive status at the last scheduled assessment or discontinuation visit.

A subject was treatment-emergent ADA positive if the subject was ADA negative at baseline and had at least one postbaseline status of ADA present with a titer of ≥ 2 times the minimum required dilution of the ADA assay (treatment induced treatment emergent ADA) or if the subject was ADA positive at baseline and had a postbaseline ADA titer 4-fold greater than the baseline titer (treatment boosted treatment emergent ADA).

A neutralizing antibody positive subject was defined as a subject who was treatment emergent ADA positive and had a positive neutralizing antibody for at least one postbaseline ADA sample.

The all-donanemab pool for the immunogenicity dataset excluded data from AACN and the long-term extension period. Per the Applicant's note in the Integrated Summary of Immunogenicity, these studies were excluded because a high proportion of subjects would have had insufficient titer data at 6 months or beyond.¹⁴³ Additionally, the Applicant noted that many subjects in Study AACN would have a single postbaseline observation for ADA. The Applicant notes that the data cutoff allowed for 52-Week data from Study AACI Safety Addendum.

Reviewer comment: Overall, this reviewer found the Applicant's approach to be acceptable.

In Study AACG, ADA samples were collected preinfusion on Weeks 0, 4, 8, 12, 16, 24, 36, 52, 76, the early discontinuation visit, and if the last scheduled assessment of immunogenicity titer was positive, during the follow up period, which was comprised of visits every 12 weeks until the titer returned to baseline or up to 48 weeks after the last dose of donanemab if the antibody titer had not returned to baseline within 48 weeks of the last dose (Weeks 88 through 124).

In Study AACH Part B, ADA samples were collected on Weeks 0, 4, 8, 16, 24, 36, 48, 60, 72, 84, 96, and the early discontinuation visit.

In Study AACI Safety Addendum, ADA samples were collected on Weeks 0, 4, 8, 12, 16, 24, 36, 52, 76, early discontinuation visit, and Weeks 84 through 120.

¹⁴³ Noted on page 33 of the Integrated Summary of Immunogenicity submitted by the Applicant on June 12, 2023.

The following table shows the treatment-emergent ADA status for the placebo-controlled period of AACI.

Table 87. Subjects with Treatment-Emergent ADA in the Placebo-controlled Period of Study AACI

	Donanemab (N = 792)	Placebo (N = 821)
Subjects evaluable for TE ADA ¹	792 (100)	821 (100)
ADA present at Baseline	50 (6.3)	56 (6.8)
Neutralizing Abs present at Baseline	29 (3.7)	34 (4.1)
Subjects postbaseline TE ADA+	691 (87.2)	48 (5.8)
Neutralizing Abs present	691 (87.2)	45 (5.5)

This table was created by Senior Clinical Analyst Dr. Rui Li.

¹A subject was considered TE ADA evaluable if they had at least one non-missing test result for the baseline period and the postbaseline period

The following table shows the treatment-emergent ADA status for the placebo-controlled pool.

Table 88. Subjects with Treatment-Emergent ADA in the Placebo-controlled Pool

	Donanemab (N = 921)	Placebo (N = 944)
Subjects evaluable for TE ADA	921 (100)	944 (100)
ADA present at Baseline	56 (6.1)	68 (7.2)
Neutralizing Abs present at Baseline	30 (3.3)	41 (4.3)
Subjects postbaseline TE ADA+	810 (87.9)	53 (5.6)
Neutralizing Abs present	810 (87.9)	50 (5.3)

This table was created by Senior Clinical Analyst Dr. Rui Li.

¹A subject was considered TE ADA evaluable if they had at least one non-missing test result for the baseline period and the postbaseline period.

The following table shows the treatment-emergent ADA status for the all-donanemab pool.

Table 89. Subjects with Treatment-Emergent ADA in the All-Donanemab Pool

	Donanemab (N =2053)
Subjects evaluable for TE ADA	2053 (100)
ADA present at Baseline	114 (5.6)
Neutralizing Abs present at Baseline	75 (3.7)
Subjects postbaseline TE ADA+	1809 (88.1)
Neutralizing Abs present	1808 (88.1)

This table was created by Senior Clinical Analyst Dr. Rui Li.

¹A subject was considered TE ADA evaluable if they had at least one non-missing test result for the baseline period and the postbaseline period.

13.18. Symptomatic ARIA-E

Analyses of symptomatic ARIA-E for this review were based on data in the adverse event dataset rather than the MRI dataset as symptoms of ARIA-E were recorded as events related to adverse events.¹⁴⁴

In the placebo-controlled period of AACI, clinical symptoms of ARIA-E resolved in 84.6% of donanemab-treated subjects (44/52). Headache, confusion, dizziness, seizure, and nausea were among the most frequently reported symptoms of ARIA-E in donanemab-treated subjects in the placebo-controlled period of AACI. The following table shows the most frequently reported symptoms of treatment-emergent ARIA-E in the donanemab-treated subjects in the placebo-controlled period of AACI.

Table 90. Reported Symptoms of Treatment-emergent ARIA-E with Incidence of at least 0.4% Higher in the Donanemab Arm Compared to Placebo in the Placebo-controlled Period of AACI

Preferred Terms	Donanemab (N = 853)	Placebo (N = 874)
Subjects Reporting Symptomatic ARIA-E	52 (6.1%)	0 (0.0%)
Subjects With Resolution of Symptomatic ARIA-E	44 (5.2%)	0 (0.0%)
Symptoms Reported with ARIA-E by Preferred Term		

¹⁴⁴These reviewer notes that symptoms of ARIA-E were recorded in the ADCE dataset, which corresponded with the ADAE dataset.

Preferred Terms	Donanemab (N = 853)	Placebo (N = 874)
Headache	24 (2.8%)	0 (0.0%)
Confusional state	13 (1.5%)	0 (0.0%)
Seizure ¹	5 (0.6%)	0 (0.0%)
Dizziness	4 (0.5%)	0 (0.0%)
Nausea	4 (0.5%)	0 (0.0%)
Fatigue	3 (0.4%)	0 (0.0%)
Gait disturbance	3 (0.4%)	0 (0.0%)
Tremor	3 (0.4%)	0 (0.0%)

This reviewer created this table using analyses by Senior Clinical Analyst Dr. Rui Li and this reviewer.

¹Includes preferred term of focal dyscognitive seizures

In the placebo-controlled pool, clinical symptoms of ARIA-E resolved in 80.7% of donanemab-treated subjects (46/57). Headache, confusion, seizure, and nausea were among the most frequently reported symptoms of ARIA-E in donanemab-treated subjects in the placebo-controlled pool. The following table shows the most frequently reported symptoms of treatment-emergent ARIA-E in the donanemab-treated subjects in the placebo-controlled pool.

Table 91. Reported Symptoms of Treatment-emergent ARIA-E with Incidence of at least 0.4% Higher in the Donanemab Arm Compared to Placebo in the Placebo-controlled Pool

Preferred Terms	Donanemab (N = 984)	Placebo (N = 999)
Subjects Reporting Symptomatic ARIA-E	57 (5.8%)	1 (0.1%)
Subjects With Resolution of Symptomatic ARIA-E	46 (4.7%)	1 (0.1%)
Symptoms Reported with ARIA-E by Preferred Term		
Headache	25 (2.5%)	1 (0.1%)
Confusional state	13 (1.3%)	0 (0.0%)
Seizure ^a	5 (0.5%)	0 (0.0%)
Nausea	4 (0.4%)	0 (0.0%)

This reviewer created this table using analyses by Senior Clinical Analyst Dr. Rui Li and this reviewer.

^aIncludes preferred term of focal dyscognitive seizures

Other less frequent reported symptoms of ARIA-E in donanemab-treated subjects in the placebo-controlled pool included fatigue, gait disturbance, tremor, asthenia, balance disorder,

delirium, visual hallucination, vomiting, abnormal behavior, acute respiratory failure,¹⁴⁵ aggression, altered state of consciousness, aphasia, ataxia, bradycardia, cerebral microhemorrhage, cognitive disorder, diplopia, disturbance in attention, hemiplegia, hypersomnia, hypertension, hypokalemia, hypomagnesemia, hypotension, illusion, imperception, incontinence, memory impairment, mental status changes, migraine, movement disorder,¹⁴⁶ paresthesia, paranasal sinus discomfort, photophobia, quadrantanopia, somnolence, speech disorder, and visual impairment.

Headache, confusional state, and dizziness were the most frequently reported symptoms of ARIA-E in the all-donanemab pool. Seizure as a symptom of ARIA-E was reported in 0.2% (6/2802) of donanemab-treated subjects.¹⁴⁷ The following table shows the most frequently reported symptoms of treatment-emergent ARIA-E in the all-donanemab pool.

Table 92. Reported Symptoms of Treatment-emergent ARIA-E with Incidence of at least 0.3% in the All-Donanemab Pool

Symptoms	Donanemab N=2802 n (%)
Total Subjects with Any Symptomatic ARIA-E	126 (4.5)
Headache	69 (2.5)
Confusional state	29 (1)
Dizziness	10 (0.4)
Gait disturbance	9 (0.3)

The reviewer created this table using the 90-Day Safety Update IDB ADCE, TELYLDFL = Y.

Per the Applicant's response dated October 13, 2022, to an information request dated October 4, 2022, severity of symptoms related to ARIA-E was not collected in Study AACG.

In the placebo-controlled period of AACI, severe symptoms of ARIA-E were reported in 1.2% (10/853), moderate in 1.4% (12/853), and mild in 3.5% (30/853) of donanemab-treated

¹⁴⁵ For the symptom of acute respiratory failure, the narrative noted that the participant developed acute respiratory failure in the setting of symptomatic ARIA-E that also caused seizure and delirium (I5T-MC-AACI- (b) (6)).

¹⁴⁶ For the symptom of movement disorder, the narrative noted that the participant was experiencing tremors in the setting of ARIA-E (I5T-MC-AACI- (b) (6)).

¹⁴⁷ Includes one participant with preferred terms of focal dyscognitive seizures and one participant (I5T-MC-AACI- (b) (6)) who did not have seizure recorded in the ADCE datasets; however, was noted to have death caused by symptomatic ARIA-E, aggravated by seizures, in a review of the narrative.

subjects. The symptoms that were associated with ARIA-E were not categorized as serious or non-serious in the trial.

In the all-donanemab pool, severe symptoms of ARIA-E were reported with similar incidence as the placebo-controlled pool (0.5% versus 1%, respectively). The most frequently reported severe symptoms of ARIA-E were seizure and confusional state, occurring in 0.2% and 0.1% of donanemab-treated subjects, respectively.

13.19. Incidence of ARIA in the All-Donanemab Pool (MRI dataset)

The following table shows the incidence of ARIA in the all-donanemab pool and is based on analyses using the MRI dataset.

Table 93. Incidence of ARIA in the All-Donanemab Pool (MRI dataset).

	Donanemab (N =2802)
ARIA	882 (31.5%)
ARIA-E	562 (20.1%)
ARIA-H	742 (26.5%)
ARIA-H, Microhemorrhages	610 (21.8%)
ARIA-H, Superficial Siderosis	330 (11.8%)

This table was created with analyses provided by Senior Clinical Analyst Dr. Rui Li using the MRI dataset.

13.20. Incidence of ARIA in Subjects in the All-Donanemab Pool Who Had Not Received Donanemab in Study AACG or the Placebo-controlled Period of AACI

The following table shows the incidence of ARIA in subjects in the all-donanemab pool who had not received donanemab in Study AACG or the placebo-controlled period of AACI and is based on analyses using the MRI dataset.

Table 94. Incidence of ARIA in Subjects in the All-Donanemab Pool Who Had Not Received Donanemab in Study AACG or the Placebo-controlled Period of AACI (MRI dataset).

	Donanemab (N =1818)
ARIA	551 (30.3%)

	Donanemab (N =1818)
ARIA-E	346 (19.0%)
ARIA-H	462 (25.4%)
ARIA-H, Microhemorrhages	381 (21.0%)
ARIA-H, Superficial Siderosis	199 (10.9%)

This table was created with analyses provided by Senior Clinical Analyst Dr. Rui Li using the MRI dataset.

13.21. Clinical Outcomes Related to ARIA

The following table summarizes ARIA events related to deaths, SAEs, study withdrawals, and treatment discontinuations for the placebo-controlled period of AACI.

Table 95. Clinical Events related to ARIA in the Placebo-controlled Period of AACI

Events	Donanemab N=853 n (%)	Placebo N=874 n (%)
ARIA ^a	307 (36.0)	122 (14.0)
Deaths ^b	3 (0.4)	0
SAEs	14 (1.6)	0
Study Withdrawal	14 (1.6)	2 (0.2)
Treatment Discontinuation	29 (3.4)	5 (0.6)
ARIA-E ^a	201 (23.6)	17 (1.9)
Deaths ^b	3 (0.4)	0
SAEs	13 (1.5)	0
Study Withdrawal	9 (1.1)	2 (0.2)
Treatment Discontinuation	21 (2.5)	3 (0.3)
Treatment Interrupted	144 (16.9)	7 (0.8)
Symptomatic ARIA-E	52 (6.1)	0
ARIA-H ^a	263 (30.8)	111 (12.7)
Deaths	2 (0.2)	0
SAEs	4 (0.5)	0
Study Withdrawal	5 (0.6)	0
Treatment Discontinuation	8 (0.9)	2 (0.2)
ARIA-H Microhemorrhage ^a	217 (25.4)	100 (11.4)
Deaths	2 (0.2)	0
SAEs	4 (0.5)	0
Study Withdrawal	4 (0.5)	0
Treatment Discontinuation	6 (0.7)	2 (0.2)

Events	Donanemab N=853 n (%)	Placebo N=874 n (%)
ARIA-H Superficial Siderosis ^a	125 (14.7)	23 (2.6)
Deaths	0	0
SAEs	0	0
Study Withdrawal	1 (0.1)	0
Treatment Discontinuation	2 (0.2)	0

The reviewer created this table using the 90Day Safety IDB ADAE dataset, TEPCLDL, APERIODC = First treatment, STUDYID = AACI

^aThe incidence of ARIA is based on analyses using the MRI dataset. The incidence of clinical outcomes of ARIA including deaths, SAEs, study withdrawals, treatment discontinuation, and symptomatic ARIA-E are based on analyses of the adverse events dataset.

^bDeaths related to ARIA and ARIA-E are based on the following subjects with fatal events related to ARIA in the placebo-controlled pool: Amyloid related imaging abnormality-edema/effusion, IST-MC-AACI- (b) (6) a case reporting the preferred term of "Death" that occurred in the setting of ARIA-E and ARIA-H, IST-MC-AACI- (b) (6) and IST-MC-AACI- (b) (6) with intracerebral hemorrhage occurring in the setting of ARIA-E and ARIA-H. For the purposes of this table, this reviewer assigned IST-MC-AACI- (b) (6) whose death was attributed to both ARIA-E and ARIA-H, and IST-MC-AACI- (b) (6) with intracerebral hemorrhage occurring in the setting of ARIA-E and ARIA-H, to both ARIA-E and ARIA-H subcategories.

The following table summarizes ARIA events related to deaths, SAEs, study withdrawals, and treatment discontinuations for the placebo-controlled pool.

Table 96. Clinical Events related to ARIA in the Placebo-controlled Pool

Events	Donanemab N=984 n (%)	Placebo N=999 n (%)
ARIA ^a	357 (36.3)	131 (13.1)
Deaths ^b	3 (0.3)	0
SAEs	16 (1.6)	0
Study Withdrawal	19 (1.9)	3 (0.3)
Treatment Discontinuation	44 (4.5)	7 (0.7)
ARIA-E ^a	236 (24.0)	18 (1.8)
Deaths ^b	3 (0.3)	0
SAEs	15 (1.5)	0
Study Withdrawal	11 (1.1)	3 (0.3)
Treatment Discontinuation	27 (2.7)	4 (0.4)
Treatment Interrupted	150 (15.2)	7 (0.7)
Symptomatic ARIA-E	57 (5.8)	1 (0.1)
ARIA-H ^a	303 (30.8)	119 (11.9)
Deaths ^b	2 (0.2)	0
SAEs	4 (0.4)	0

Events	Donanemab N=984 n (%)	Placebo N=999 n (%)
Study Withdrawal	8 (0.8)	0
Treatment Discontinuation	17 (1.7)	3 (0.3)
ARIA-H Microhemorrhage ^a	243 (24.7)	105 (10.5)
Deaths	2 (0.2)	0
SAEs	4 (0.4)	0
Study Withdrawal	6 (0.6)	0
Treatment Discontinuation	9 (0.9)	2 (0.2)
ARIA-H Superficial Siderosis ^a	147 (14.9)	26 (2.6)
Deaths	0	0
SAEs	0	0
Study Withdrawal	2 (0.2)	0
Treatment Discontinuation	8 (0.8)	1 (0.1)

The reviewer created this table using analyses by Senior Clinical Analyst Dr. Rui Li.

^aThe incidence of ARIA is based on analyses using the MRI dataset. The incidence of clinical outcomes of ARIA including deaths, SAEs, study withdrawals, treatment discontinuation, and symptomatic ARIA-E are based on analyses of the adverse events dataset.

^bDeaths related to ARIA and ARIA-E are based on the following subjects with fatal events related to ARIA: Amyloid related imaging abnormality-edema/effusion, I5T-MC-AACI- (b) (6) a case reporting the preferred term of “Death” that occurred in the setting of ARIA-E and ARIA-H, I5T-MC-AACI- (b) (6) and I5T-MC-AACI- (b) (6) with intracerebral hemorrhage occurring in the setting of ARIA-E and ARIA-H. For the purposes of this table, this reviewer assigned I5T-MC-AACI- (b) (6) whose death was attributed to both ARIA-E and ARIA-H, and I5T-MC-AACI- (b) (6) with intracerebral hemorrhage occurring in the setting of ARIA-E and ARIA-H, to both the subcategories of ARIA-E and ARIA-H.

13.22. MRI Classification for ARIA

The following table shows the MRI classification used for ARIA events in Study AACI.

Table 97. Radiographic Severity of ARIA in Study AACI

ARIA Type	Radiographic Severity		
	Mild	Moderate	Severe
ARIA-E	FLAIR hyperintensity confined to sulcus and/or cortex/subcortex white matter in one location <5 cm.	FLAIR hyperintensity 5 to 10 cm in single greatest dimension, or more than 1 site of involvement, each measuring < 10 cm.	FLAIR hypersensitivity > 10 cm with associated gyral swelling and sulcal effacement. One or more separate/independent sites of involvement may be noted.

ARIA Type	Radiographic Severity		
	Mild	Moderate	Severe
ARIA-H Microhemorrhage	≤ 4 treatment-emergent total microhemorrhages and new incident microhemorrhages	5-9 treatment-emergent total microhemorrhages or new incident microhemorrhages, whichever is greater	≥ 10 treatment-emergent Total microhemorrhages or new incident microhemorrhages, whichever is greater
ARIA-H Superficial Siderosis	1 new or increased focal area of superficial siderosis	2 new or increased focal areas of superficial siderosis	> 2 new or increased focal areas of superficial siderosis

The above table is copied from the ISAP submitted by the Applicant on June 12, 2023 (page 38).

Reviewer comment: Overall, this reviewer found the Applicant's approach to be acceptable.

In Studies AACH, AACI Safety Addendum, and AACN, similar ARIA-E severity rating scales were used except that moderate ARIA-E was further subdivided into the categories of mild+, moderate, and moderate+. ¹⁴⁸

Similar ARIA-H severity rating scales were used for Study AACH, AACI, and AACN. ¹⁴⁹

Dose Modifications Based on ARIA

The following figure shows dosing recommendations based on presence of ARIA in Study AACI. The reader is referred to this reviewer's review of the initial donanemab submission, dated January 17, 2023, for dosing recommendations based on ARIA for Studies AACG, AACH, and AACN (page 199).

¹⁴⁸ Noted in Appendices 1, 2, and 3, in a response dated October 13, 2022, to an information request dated October 4, 2022.

¹⁴⁹ Noted by the Applicant in a response dated October 13, 2022, an information request by the Agency dated October 4, 2022.

Figure 6. Dosing Recommendations Based on ARIA in Study AACI

Finding	Symptoms	MRI Severity	Guidance
ARIA-E*	Asymptomatic	Mild to Moderate Severity rating 1-3	- Hold IP if severity 3 and occurs within first 3 doses of the double-blind or long-term extension period, otherwise may continue IP - Monitor with unscheduled MRIs monthly until resolution
		Moderate + to Severe Severity rating 4-5	- Hold IP - Monitor with unscheduled MRIs monthly - Upon resolution of ARIA-E on imaging, consider re-initiating IP - If resolution is not observed, permanently discontinue IP, but continue other study activities
	Symptomatic	Any Severity	- Hold IP - Monitor with unscheduled MRIs monthly - Upon resolution of ARIA-E on imaging and resolution of clinical symptoms, consider re-initiating IP - If resolution of ARIA-E or resolution of symptoms are not observed, permanently discontinue IP, but continue other study activities - If ARIA-E symptoms are clearly related to an SAE, then permanently discontinue IP, but continue other study activities
ARIA-H ^b Microhemorrhage (MCH), Superficial Siderosis	Asymptomatic	≤ 10 new MCH from baseline and/or ≤ 2 Superficial Sideroses	- Hold IP if > 4 new MCH or ≥1 new Superficial Siderosis within first 3 doses of the double-blind or long-term extension period, otherwise may continue IP - Monitor with unscheduled MRIs monthly
		>10 new MCH from baseline and/or >2 Superficial Sideroses	- Hold IP - Monitor with unscheduled MRIs monthly - Upon stabilization of ARIA-H on imaging, consider re-initiating IP (stabilization defined as no new/increased superficial siderosis and not more than 1 new microhemorrhage on subsequent MRI)
	Symptomatic	Any Severity	- Hold IP - Monitor with unscheduled MRIs monthly - If resolution of symptoms is not observed, permanently discontinue IP, but continue other study activities - If ARIA-H symptoms are clearly related to an SAE, then permanently discontinue IP, but continue other study activities
ARIA-H Macrohemorrhage	Asymptomatic or Symptomatic	Any Severity	- Permanently discontinue IP, but continue other study activities - Monitor with unscheduled MRIs monthly

The above figure was taken from the Applicant's information response dated July 18, 2022, to an information request dated July 15, 2022 (page 221).

In Study AACG, treatment was permanently discontinued for prolonged acute infusion reaction and for ARIA events including: a second incidence of ARIA-E after previous dose reduction or temporary discontinuation; any increase in ARIA-H accompanied by clinically significant symptoms; > 4 new microhemorrhages, > 1 new area of superficial siderosis or significant worsening of pre-existing superficial siderosis, or any macrohemorrhage regardless of symptoms; or an ARIA-E event reported as an SAE.¹⁵⁰

¹⁵⁰ Noted on page 56 of the AACG Protocol (version d) submitted May 18, 2022.

13.23. Incidence of Intracerebral Hemorrhage > 1 cm in the Placebo-Controlled Pool

The following table shows the incidence of intracerebral hemorrhage > 1 cm in the placebo-controlled pool using the MRI and adverse event datasets combined.

Table 98. Incidence of Intracerebral Hemorrhage > 1 cm in the Placebo-Controlled Pool (MRI and Adverse Events dataset).

	Donanemab (N = 984)	Placebo (N = 999)
Intracerebral hemorrhage > 1 cm ^a	4 (0.4%)	2 (0.2%)

This table was created by combining analyses provided by Senior Clinical Analyst Dr. Rui Li using the MRI dataset with analyses provided by this reviewer using the adverse events dataset.

^aThe donanemab arm includes 3 subjects identified from the MRI dataset: IST-MC-AACI- (b) (6), IST-MC-AACI- (b) (6), and IST-MC-AACI- (b) (6), and 1 subject identified from the adverse event dataset: IST-MC-AACI- (b) (6) (based on review of the narrative, which indicated that the subject had a 5.5 x 4.3 cm hematoma in the left posterior parietal region noted on a CT scan). The placebo arm includes 2 subjects identified from the MRI dataset: IST-MC-AACI- (b) (6) and IST-MC-AACI- (b) (6). These numbers do not include two donanemab-treated subjects and two placebo-treated subjects from the adverse event where the size was not indicated (Donanemab arm: subarachnoid hemorrhage, IST-MC-AACI- (b) (6) and subarachnoid hemorrhage, IST-MC-AACI- (b) (6). Placebo arm: subarachnoid hemorrhage, IST-MC-AACI- (b) (6) and cerebral hematoma, IST-MC-AACI- (b) (6)).

13.24. Events of Intracranial Hemorrhage

The following table lists subjects in the all-donanemab pool with intracerebral hemorrhage, thalamus hemorrhage, subarachnoid hemorrhage, and cerebral hematoma based on a review of the adverse event and MRI datasets. The table also includes a subject with intracerebral hemorrhages and subarachnoid hemorrhage occurring more than 57 days after the last dose of donanemab and who also had co-occurring ARIA that had started within 57 days of the last dose of donanemab (IST-MC-AACI- (b) (6)).

Table 99. Subjects with Events of Intracranial Hemorrhage in the MRI dataset or the Adverse Event Dataset.

USUBJID Study	Event of Intracerebral Hemorrhage	Risk Factors	Abnormal Screening MRI Findings Postbaseline ARIA Events ^a	Comments
Intracerebral Hemorrhage with Size > 1 cm				
IST-MC-AACI- (b) (6) (b) (6)	Thalamus Hemorrhage	PMH: HTN	Screening MRI: Beginning of confluence of lesions of white matter disease	Fatal Case The subject's past medical history of

USUBJID Study	Event of Intracerebral Hemorrhage	Risk Factors	Abnormal Screening MRI Findings Postbaseline ARIA Events ^a	Comments
AACI Safety Addendum				hypertension was a likely risk factor for event.
I5T-MC- AACI- (b) (6) (b) (6) LTE of AACI	Intracerebral hemorrhage	• ε3/ε4 • CM: Tenecteplase 22 mg once	• Screening MRI: Focal lesions of white matter disease • Postbaseline ARIA events: ARIA-E and ARIA-H SS (70 mm)	Fatal Case Occurred in the setting of thrombolytic therapy and ARIA-E
I5T-MC- AACI- (b) (6) (b) (6) AACI Safety Addendum	Intracerebral hemorrhage	• ε3/ε4 • PMH: HTN • CM: ASA 81 mg daily	• Screening MRI: Focal lesions of white matter disease • Postbaseline ARIA events: ARIA-E, ARIA-H Mh (1), and ARIA-H SS (20 mm)	ARIA-E, ARIA-H Mh (1) and SS (20 mm) on SD 71 in same location as intracerebral hemorrhage on SD 99.
I5T-MC- AACI- (b) (6) (b) (6) LTE of AACI	Two separate events of intracerebral hemorrhages (one on SD 625 and on SD 703), subarachnoid hemorrhage (SD 645)	• ε4/ε4 • CM: ASA 325 mg daily • Possible risk factor of elevated blood pressure (noted in ER upon presentation for SAH)	• Screening MRI: Focal lesions of white matter disease • The last MRI findings prior to starting treatment with donanemab: superficial siderosis (15 mm), and focal lesions of white matter disease • Postbaseline ARIA events: ARIA-E, ARIA-H Mh (31), and ARIA-H SS (75 mm)	Events Occurred > 57 Days from Last Dose SD 547: First (and only) dose of donanemab SD 569: severe ARIA-E SD 625: MRI with intracerebral hemorrhage (left frontal lobe, 11 mm), ARIA-E (bilateral frontal and temporal lobes, right occipital and parietal lobes), ARIA-H microhemorrhage (> 10 new Mh (total 31), ARIA- H SS (increased in size [right parietal lobe, 75 mm; right temporal lobe,

USUBJID Study	Event of Intracerebral Hemorrhage	Risk Factors	Abnormal Screening MRI Findings Postbaseline ARIA Events ^a	Comments
				50 mm] and new SS [right frontal, 50 mm]). SD 645: subarachnoid hemorrhage SD 703: MRI with intracerebral hemorrhage of 85 mm (right frontal lobe, initial identification), ARIA-E (right frontal and parietal lobes), ARIA-H Mh (presence of 3 new microhemorrhages), ARIA-H SS (increased in size [right parietal, temporal, and frontal lobes] and newly identified [left frontal lobe, 80 mm]), and bilateral frontal subdural hematomas (initial identification).
I5T-MC-AACI- (b) (6) (b) (6) PC of AACI	Intracerebral hemorrhage	• $\epsilon 3/\epsilon 4$ • CM: Prasugrel 10 mg daily	• Screening MRI: Focal lesions of white matter disease • Postbaseline ARIA events: ARIA-E, ARIA-H Mh (2) and ARIA-H SS (14 mm)	ARIA-E and SS on SD 74 in the same area of intracerebral hemorrhage on SD 192
I5T-MC-AACI- (b) (6) (b) (6) LTE of AACI	Intracerebral hemorrhage	• $\epsilon 3/\epsilon 4$	• Screening MRI: Focal lesions of white matter disease, one microhemorrhage	An MRI on SD 618 showed a 13 mm intracerebral hemorrhage in the right temporal lobe (3 days after the 3 rd donanemab infusion).

USUBJID Study	Event of Intracerebral Hemorrhage	Risk Factors	Abnormal Screening MRI Findings Postbaseline ARIA Events ^a	Comments
				The subject was reported to have been asymptomatic and on SD 623, donanemab was discontinued. The mean blood pressure value in the 6 study visits in the preceding 6 months before the event of intracerebral hemorrhage was 119/76 mmHg (range: 114 to 124 /69 to 80 mmHg)
I5T-MC- AACI- (b) (6) (b) (6) AACI Safety Addendum	Intracerebral hemorrhage	• ε3/ε4 • PMH: HTN • CM: Apixaban 5 mg bid • Fall	• Screening MRI: Beginning of confluence of lesions of white matter disease • Postbaseline ARIA events: ARIA-E	Pt had an intracerebral hemorrhage of unidentified size (right occipital lobe, SD 74) within 57 days of the last dose of donanemab (in the adverse event dataset) and an intracerebral hemorrhage > 1 cm > 57 days from the last dose of donanemab (MRI dataset). On SD 67, pt had ARIA-E (cerebellum and parietal lobes and right frontal lobe) and a lacunar infarct (right cerebellum)
I5T-MC- AACI- (b) (6) (b) (6) PC of AACI	Intracerebral hemorrhage	• ε3/ε4 • PMH: HTN	• Screening MRI: Focal lesions of white matter disease	ARIA-E on SD 71 in the same location as intracerebral hemorrhage on SD 526. Also ARIA-E and 3 Mh in

USUBJID Study	Event of Intracerebral Hemorrhage	Risk Factors	Abnormal Screening MRI Findings Postbaseline ARIA Events ^a	Comments
			Postbaseline ARIA events: ARIA-E, ARIA-H Mh (3), and ARIA-H SS (20 mm)	the same location as the intracerebral hemorrhage on SD 526.
I5T-MC-AACI- (b) (6) (b) (6) PC of AACI	Hemorrhagic stroke	- ε3/ε4 - Elevated blood pressure in study	Screening MRI: Focal lesions of white matter disease, SS (25 mm)	Blood pressure at the two study visits preceding the vent was 142/82 and 146/88 mmHg.
I5T-MC-AACI- (b) (6) (b) (6) PC of AACI	Hemorrhagic stroke and Hematoma 5.5 x 4.3 cm	- PMH: HTN - CM: Several acetylsalicylic acid tablets (amount not specified)	- Screening MRI: Beginning of confluence of lesions of white matter disease, SS (50 mm) - Postbaseline ARIA events: ARIA-E, ARIA-H Mh (1), and ARIA-H SS (65 mm)	Fatal Case where death certificate listed both ARIA-H and hemorrhagic stroke as the cause of death Had ARIA-E in the same location as hematoma. ARIA-E on SD 71 (included left parietal area). Hematoma (left parietal) noted on SD 72 based on review of the narrative, (5.5 x 4.3 cm)
I5T-MC-AACI- (b) (6) (b) (6) AACI Safety Addendum	Cerebral hematoma	- ε3/ε4 - PMH: HTN	- Screening MRI: Focal lesions of white matter disease - Postbaseline ARIA events: ARIA-E and ARIA-H Mh (3)	The subject had ongoing ARIA-E (right parietal, temporal lobes) and ARIA-H Mh (1 new Mh with a total of 2 Mh) on SD 51 The AE of cerebral hematoma (2 x 3 cm, left parietal) and fall were reported on SD 93

USUBJID Study	Event of Intracerebral Hemorrhage	Risk Factors	Abnormal Screening MRI Findings Postbaseline ARIA Events ^a	Comments
				This reviewer notes that given the AE of fall reported on the same day, this cerebral hematoma may represent a subdural hematoma
Intracerebral Hemorrhage, Size Not Reported				
I5T-MC-AACI- (b) (6) PC of AACI	Subarachnoid hemorrhage	- PMH: HTN - CM: ASA 81 mg daily - Fall	Screening MRI: Focal lesions of white matter disease, superficial siderosis of 17 mm	
I5T-MC-AACI- (b) (6) PC of AACI	Subarachnoid hemorrhage	- PMH: HTN, unsteadiness - CM: ASA 81 mg daily - Fall	Screening MRI: Focal lesions of white matter disease	Fatal Case Fall from a ladder was a likely contributory factor The last dose of donanemab was 75 days prior to the event. The fatal event occurred 15 days after last dose of placebo as the subject had been switched to placebo per protocol.
I5T-MC-AACI- (b) (6) AACI Safety Addendum	Subarachnoid hemorrhage	PMH: HTN	- Screening MRI: Focal lesions of white matter disease - Postbaseline ARIA events: ARIA-H SS (14 mm)	
I5T-MC-AACI- (b) (6)	Cerebral hematoma	- ε3/ε4 - PMH: HTN	Screening MRI: Focal lesions of white matter disease	

USUBJID Study	Event of Intracerebral Hemorrhage	Risk Factors	Abnormal Screening MRI Findings Postbaseline ARIA Events ^a	Comments
AACI Safety Addendum				
I5T-MC- AACI- (b) (6) (b) (6) AACI Safety Addendum	Hemorrhagic stroke	• ε3/ε4 • PMH: HTN • CM: Clopidogrel 75 mg daily	• Screening MRI: Focal lesions of white matter disease • Postbaseline ARIA events: ARIA-E, ARIA-H Mh (2), lacunar infarct, and presence of shunt	Also had lacunar infarct and presence of shunt on MRI

CM: concomitant medication, HTN: hypertension, Mh: microhemorrhage, PMH: past medical history, SAH: subarachnoid hemorrhage, SD: study day, SS: superficial siderosis

^aPostbaseline ARIA Events Prior to Intracerebral Hemorrhage and up to 30 Days After (identified using the MRI and adverse event datasets).

13.25. Clinical Outcomes of TEAEs Belonging to the EMQ/FMQ Grouping of Intracranial Hemorrhage

The following table shows the incidence of TEAEs belonging to the EMQ/FMQ grouping of Intracranial Hemorrhage by preferred terms in the placebo-controlled period of AACI.

Table 100. TEAEs of EMQ/FMQ Grouping of Intracranial Hemorrhage in the Placebo-controlled Period of AACI

Events	Donanemab N=853 n (%)	Placebo N=874 n (%)
TEAEs ¹	25 (2.9)	17 (1.9)
Subdural hematoma	4 (0.5)	1 (0.1)
Cerebral microhemorrhage	16 (1.9)	13 (1.5)
Intracerebral hemorrhage	2 (0.2)	1 (0.1)
Subarachnoid hemorrhage	2 (0.2)	1 (0.1)
Hemorrhagic stroke	1 (0.1)	1 (0.1)
Cerebral hematoma	0	1 (0.1)

This reviewer created this table using the 90-Day Safety Update ADAE dataset, TEPCLDL = Y, APERIODC = First Treatment period, STUDYID = AACI.

¹This does not include a fatal case of ARIA-H in a donanemab-treated subject who also had intracerebral hemorrhage and ARIA-E (ARIA-H, IST-MC-AACI- (b) (6)).

The following table shows the incidence of TEAEs belonging to the EMQ/FMQ grouping of Intracranial Hemorrhage by preferred terms in the placebo-controlled pool.

Table 101. TEAEs of EMQ/FMQ Grouping of Intracranial Hemorrhage in the Placebo-controlled Pool

Events	Donanemab N=984 n (%)	Placebo N=999 n (%)
TEAEs ¹	36 (3.7)	21 (2.1)
Cerebral microhemorrhage	26 (2.6)	16 (1.6)
Subdural hematoma	5 (0.5)	1 (0.1)
Cerebral hemorrhage	2 (0.2)	1 (0.1)
Extradural hematoma	1 (0.1)	0
Subarachnoid hemorrhage	2 (0.2)	1 (0.1)
Hemorrhagic stroke	1 (0.1)	1 (0.1)
Cerebral hematoma	0	1 (0.1)
Intraventricular hemorrhage	0	1 (0.1)

This reviewer created this table using the 90-Day Safety Update ADAE dataset, TEPCLDL = Y, APERIODC = First Treatment period.

¹This does not include a fatal case of ARIA-H in a donanemab-treated subject who also had intracerebral hemorrhage and ARIA-E (ARIA-H, IST-MC-AACI- (b) (6)).

The reader is referred to the [Deaths section](#) of this review for narratives related to events of intracranial hemorrhage with fatal outcome.

TEAEs belonging to the EMQ/FMQ grouping of Intracranial Hemorrhage were serious in 0.7% (6/853) of donanemab-treated subjects in the placebo-controlled period of AACI. A similar incidence was observed in the all-donanemab pool (0.2% [7/2802]). The reader is referred to the Narratives section of the [Serious Adverse Events](#) section of this review for a review of narratives of serious cases of intracranial hemorrhage.

TEAEs belonging to the EMQ/FMQ grouping of Intracranial Hemorrhage were reported to lead to study withdrawal in 0.2% (2/853) and treatment discontinuation in 0.5% (4/853) of donanemab-treated subjects in the placebo-controlled period of AACI. Similar incidences were observed in the all-donanemab pool (difference no greater than 0.1%).

The following table summarizes clinical outcomes of TEAEs belonging to the EMQ/FMQ Grouping of Intracranial Hemorrhage in the placebo-controlled period of AACI.

Table 102. Clinical Outcomes of TEAEs Belonging to EMQ/FMQ Grouping of Intracranial Hemorrhage in the Placebo-controlled Period of AACI

Events	Donanemab N=853 n (%)	Placebo N=874 n (%)
TEAEs ¹	25 (2.9)	17 (1.9)
Deaths ¹	1 (0.1)	0
Subarachnoid hemorrhage	1 (0.1)	0
SAEs ¹	6 (0.7)	2 (0.2)
Subdural hematoma	3 (0.4)	0
Subarachnoid hemorrhage	2 (0.2)	1 (0.1)
Hemorrhagic stroke	1 (0.1)	1 (0.1)
Treatment Discontinuation	4 (0.5)	2 (0.2)
Intracerebral hemorrhage	1 (0.1)	0
Subarachnoid hemorrhage	1 (0.1)	0
Subdural hematoma	1 (0.1)	0
Hemorrhagic stroke	1 (0.1)	1 (0.1)
Cerebral microhemorrhage	0	1 (0.1)

This reviewer created this table using the 90-Day Safety Update ADAE dataset, TEPCLDL = Y, APERIODC = First Treatment period, STUDYID = AACI. Deaths: DTHAEFL = Y. Serious events: AESER = Y. Treatment status: AEACN = treatment withdrawn.

¹This does not include a fatal case of ARIA-H in a donanemab-treated subject who also had intracerebral hemorrhage and ARIA-E (ARIA-H, IST-MC-AACI- (b) (6)).

The following table summarizes clinical outcomes of TEAEs belonging to the EMQ/FMQ grouping of Intracranial Hemorrhage in the placebo-controlled pool.

Table 103. Clinical Outcomes of TEAEs Belonging to EMQ/FMQ Grouping of Intracranial Hemorrhage in the Placebo-controlled Pool

Events	Donanemab N=984 n (%)	Placebo N=999 n (%)
TEAEs ¹	36 (3.7)	21 (2.1)
Deaths ¹	1 (0.1)	0
Subarachnoid hemorrhage	1 (0.1)	0
SAEs ¹	7 (0.7)	2 (0.2)
Subdural hematoma	4 (0.4)	1 (0.1)
Extradural hematoma	1 (0.1)	0
Subarachnoid hemorrhage	2 (0.2)	1 (0.1)
Hemorrhagic stroke	1 (0.1)	1 (0.1)
Treatment Discontinuation	7 (0.7)	2 (0.2)

Events	Donanemab N=984 n (%)	Placebo N=999 n (%)
Cerebral microhemorrhage	3 (0.3)	1 (0.1)
Intracerebral hemorrhage	1 (0.1)	0
Subarachnoid hemorrhage	1 (0.1)	0
Subdural hematoma	1 (0.1)	0
Hemorrhagic stroke	1 (0.1)	1 (0.1)

This reviewer created this table using the 90-Day Safety Update ADAE dataset, TEPCLDL = Y, APERIODC = First Treatment period. Deaths: DTHAEFL = Y. Serious events: AESER = Y. Treatment status: AEACN = treatment withdrawn.

¹This does not include a fatal case of ARIA-H in a donanemab-treated subject who also had intracerebral hemorrhage and ARIA-E (ARIA-H, IST-MC-AACI- (b) (6)).

13.26. Maximum Radiographic Severity of ARIA in the Placebo-Controlled Pool and the All-Donanemab Pool

The following table shows maximum radiographic severity of ARIA in the placebo-controlled pool.

Table 104. Maximum Radiographic Severity of ARIA in the Placebo-controlled Pool (MRI dataset)

	Severity	Donanemab (N = 984)	Placebo (N = 999)
Total Subjects with any ARIA (-E or H)	Questionable	0 (0.0%)	0 (0.0%)
	Mild	141 (14.3%)	107 (10.7%)
	Moderate	118 (12.0%)	21 (2.1%)
	Severe	98 (10.0%)	3 (0.3%)
	Total	357 (36.3%)	131 (13.1%)
ARIA-E	Questionable	1 (0.1%)	0 (0.0%)
	Mild	70 (7.1%)	14 (1.4%)
	Moderate	144 (14.6%)	4 (0.4%)
	Severe	21 (2.1%)	0 (0.0%)
	Total	236 (24.0%)	18 (1.8%)
ARIA-H	Questionable	0 (0.0%)	0 (0.0%)
	Mild	157 (16.0%)	99 (9.9%)
	Moderate	55 (5.6%)	17 (1.7%)
	Severe	91 (9.2%)	3 (0.3%)
	Total	303 (30.8%)	119 (11.9%)
ARIA-H, Microhemorrhages	Questionable	0 (0.0%)	0 (0.0%)
	Mild	163 (16.6%)	93 (9.3%)
	Moderate	35 (3.6%)	11 (1.1%)
	Severe	45 (4.6%)	1 (0.1%)
	Total	243 (24.7%)	105 (10.5%)
ARIA-H, Superficial Siderosis	Questionable	0 (0.0%)	0 (0.0%)
	Mild	56 (5.7%)	18 (1.8%)

	Severity	Donanemab (N = 984)	Placebo (N = 999)
	Moderate	36 (3.7%)	6 (0.6%)
	Severe	55 (5.6%)	2 (0.2%)
	Total	147 (14.9%)	26 (2.6%)

This table was created by Senior Clinical Analyst Dr. Rui Li.

The following table shows maximum radiographic severity of ARIA in the all-donanemab pool.

Table 105. Maximum Radiographic Severity of ARIA in the All-Donanemab Pool (MRI dataset)

	Severity	Donanemab (N =2802)
Total Subjects with any ARIA (-E or H)	Questionable	0 (0.0%)
	Mild	398 (14.2%)
	Moderate	262 (9.4%)
	Severe	222 (7.9%)
	Total	882 (31.5%)
ARIA-E	Questionable	1 (0.0%)
	Mild	188 (6.7%)
	Moderate	325 (11.6%)
	Severe	48 (1.7%)
	Total	562 (20.1%)
ARIA-H	Questionable	0 (0.0%)
	Mild	425 (15.2%)
	Moderate	113 (4.0%)
	Severe	204 (7.3%)
	Total	742 (26.5%)
ARIA-H, Microhemorrhages	Questionable	0 (0.0%)
	Mild	417 (14.9%)
	Moderate	82 (2.9%)
	Severe	111 (4.0%)
	Total	610 (21.8%)
ARIA-H, Superficial Siderosis	Questionable	0 (0.0%)
	Mild	140 (5.0%)
	Moderate	75 (2.7%)
	Severe	115 (4.1%)
	Total	330 (11.8%)

This table was created by Senior Clinical Analyst Dr. Rui Li.

13.27. Isolated ARIA-E and ARIA-H

In the placebo-controlled period of AACI, isolated ARIA-E was reported in 5.2% of donanemab-treated subjects compared to 1.3% on placebo. Isolated ARIA-H occurred with similar incidence in donanemab and placebo arms (12.4% versus 12.0%, respectively).

The following table shows the incidence of isolated ARIA-E and isolated ARIA-H in the placebo-controlled period of AACI.

Table 106. Incidence of Isolated ARIA in the Placebo-Controlled Period of AACI (MRI dataset).

	Donanemab (N = 853)	Placebo (N = 874)
Overall ARIA	307 (36.0)	122 (14.0)
ARIA-E	201 (23.6)	17 (1.9)
Isolated ARIA-E	44 (5.2)	11 (1.3)
ARIA-H	263 (30.8)	111 (12.7)
Isolated ARIA-H	106 (12.4)	105 (12.0)

This table was created by Senior Clinical Analyst Dr. Rui Li.

Isolated TE ARIA-E: A subject who had at least one MRI with treatment-emergent ARIA-E and no MRIs with treatment-emergent ARIA-H.

Isolated TE ARIA-H: A subject who had at least one MRI with treatment-emergent ARIA-H and no MRIs with treatment-emergent ARIA-E.

In the placebo-controlled pool, isolated ARIA-E was reported in 5.5% of donanemab-treated subjects compared to 1.2% on placebo. Isolated ARIA-H occurred with similar incidence in donanemab and placebo arms (12.3% versus 11.3%, respectively).

The following table shows the incidence of isolated ARIA-E and isolated ARIA-H in the placebo-controlled pool.

Table 107. Incidence of Isolated ARIA in the Placebo-Controlled Pool (MRI dataset).

	Donanemab (N = 984)	Placebo (N = 999)
Overall ARIA	357 (36.3)	131 (13.1)
ARIA-E	236 (24.0)	18 (1.8)
Isolated ARIA-E	54 (5.5)	12 (1.2)
ARIA-H	303 (30.8)	119 (11.9)
Isolated ARIA-H	121 (12.3)	113 (11.3)

	Donanemab (N = 984)	Placebo (N = 999)

This table was created by Senior Clinical Analyst Dr. Rui Li.

Isolated TE ARIA-E: A subject who had at least one MRI with treatment-emergent ARIA-E and no MRIs with treatment-emergent ARIA-H.

Isolated TE ARIA-H: A subject who had at least one MRI with treatment-emergent ARIA-H and no MRIs with treatment-emergent ARIA-E.

In the all-donanemab pool, isolated ARIA-E and isolated ARIA-H were reported with similar incidence compared to the placebo-controlled pool (ARIA-E: 5.0% versus 5.2% and ARIA-H: 11.4% versus 12.4%, respectively).

13.28. ARIA-E by Number of Doses Received for the Placebo-Controlled Pool

In the placebo-controlled pool, approximately 58% of donanemab-treated subjects had developed ARIA-E before the fourth dose of donanemab and 88% of subjects before the 7th dose. ARIA-E was noted to occur as late as after the 19th dose in the placebo-controlled pool.

The following table shows the number of doses donanemab-treated subjects received prior to developing the first episode of ARIA-E in the placebo-controlled pool.

Table 108. Number of Doses Prior to First ARIA-E in Donanemab-Treated Subjects in the Placebo-controlled pool (MRI dataset).

Number of Dose Prior to ARIA-E	First ARIA-E Subject Numbers	Cumulative First ARIA-E Subject Numbers N(%)
1	8	8 (3.4)
2	25	33 (14.0)
3	104	137 (58.1)
4	8	145 (61.4)
5	10	155 (65.7)
6	52	207 (87.7)
7	11	218 (92.4)
9	1	219 (92.8)
10	3	222 (94.1)
11	1	223 (94.5)
13	11	234 (99.2)
14	1	235 (99.6)
19	1	236 (100)

This table was created by Senior Clinical Analyst Dr. Rui Li.

13.29. ARIA-H by Number of Doses Received for the Placebo-Controlled Pool

In the placebo-controlled pool, approximately 43% of donanemab-treated subjects had developed ARIA-H before the fourth dose of donanemab and 71% of subjects before the

seventh dose. ARIA-H was noted to occur as late as after the 19th dose. The following table shows the number of doses donanemab-treated subjects received prior to developing ARIA-H in the placebo-controlled pool.

Table 109. Number of Doses Prior to ARIA-H in Donanemab-Treated Subjects in the Placebo-controlled pool (MRI dataset).

Number of Dose Prior ARIA-H	First ARIA-H Subject Numbers	Cumulative First ARIA-H Subject Numbers N(%)
1	7	7 (2.3)
2	18	25 (8.3)
3	104	129 (42.6)
4	5	134 (44.2)
5	12	146 (48.2)
6	69	215 (71.0)
7	16	231 (76.2)
8	3	234 (77.2)
9	5	239 (78.9)
10	1	240 (79.2)
11	4	244 (80.5)
12	6	250 (82.5)
13	30	280 (92.4)
14	7	287 (94.7)
16	1	288 (95.0)
17	1	289 (95.4)
19	14	303 (100)

This table was created by Senior Clinical Analyst Dr. Rui Li.

13.30. Time to First Episode of ARIA-E

The following table shows the time in days to the first episode of ARIA-E in the placebo-controlled period of AACI.

Table 110. Time (Days) to First Episode of ARIA-E in the Placebo-Controlled Period of AACI (MRI dataset)

Statistics	Donanemab (N = 853)	Placebo (N = 874)
N	201	17
Mean	57.34	40.12
SD	35.27	21.59
Median	47.00	35.00
Min	9.0	7.0
Max	286.0	85.0
95% CI	52.4- 62.2	29.0- 51.2

Statistics	Donanemab (N = 853)	Placebo (N = 874)

This table was created by Senior Clinical Analyst Dr. Rui Li.

The following table shows the time in days to the first episode of ARIA-E in the placebo-controlled pool.

Table 111. Time (Days) to First Episode of ARIA-E in the Placebo-controlled Pool (MRI dataset)

Statistics	Donanemab (N = 984)	Placebo (N = 999)
N	236	18
Mean	58.45	41.06
SD	35.54	21.32
Median	48.50	37.00
Min	9.0	7.0
Max	286.0	85.0
95% CI	53.9- 63.0	30.5- 51.7

This table was created by Senior Clinical Analyst Dr. Rui Li.

Similar findings for median time to first episode of ARIA-E were observed for the all-donanemab pool compared to the placebo-controlled period of AACI (median: 44 days, minimum: 0 days, maximum 394 days).

13.31. Time to Resolution of First Event of ARIA-E for the Placebo-Controlled Pool

In donanemab-treated subjects in the placebo-controlled pool, 62% of subject's first ARIA-E event resolved by the 12th week and 78% by the 20th week.

The following table shows the time to resolution of the first event of ARIA-E for the pooled placebo-controlled period.

Table 112. Time to Resolution of First Event of ARIA-E for the Placebo-Controlled Pool.

Time to Resolution	Donanemab (N = 236)		Placebo (N = 18)	
	No. of First ARIA-E Resolved	Cumulative First ARIA-E Resolved N(%)	No. of First ARIA-E Resolved	Cumulative First ARIA-E Resolved N(%)
<= 12 Weeks	146	146 (61.9)	6	6 (33.3)
<= 20 Weeks	39	185 (78.4)	1	7 (38.9)
End of Study	7	192 (81.4)	0	7 (38.9)

This table was created by Senior Clinical Analyst Dr. Rui Li.

13.32. Time to Resolution of ARIA-E in Days in the Placebo-Controlled Pool

The following table shows time to resolution for ARIA-E events in the placebo-controlled pool.

Table 113. Time to Resolution of ARIA-E in the Placebo-controlled Pool¹

	Donanemab N=984	Placebo N=999
Number of ARIA-E events, n	244	7
Mean (SD)	62.3 (35.8)	42.7 (23.6)
Median (Min, Max)	57 (15, 287)	29 (25, 85)

The reviewer created this table using the ADTTE dataset (sequence 137), PARAM = Time of ARIA-E Resolution (Days) - PC Last Dose + 57 days, EVNTDESC: Safety MRI ARIA-E resolution. SD: standard deviation.

¹This calculation includes only ARIA-E events that had resolved at the time of the data cutoff.

13.33. Subjects with Multiple Episodes of ARIA-E in the Placebo-Controlled Pool

In the placebo-controlled pool, approximately 5.5% of donanemab-treated subjects who developed ARIA-E had 3 or more episodes of ARIA-E.

The following table shows the incidence of subjects with multiple episodes of ARIA-E in the placebo-controlled pool.

Table 114. Incidence of Subjects with Multiple Episodes of ARIA-E in the Placebo-controlled Pool

Number of ARIA-E Episodes	Donanemab (N = 236)	Placebo (N = 18)
1	184 (78.0)	18 (100)

Number of ARIA-E Episodes	Donanemab (N = 236)	Placebo (N = 18)
2	39 (16.5)	0 (0.0)
3	7 (3.0)	0 (0.0)
4	6 (2.5)	0 (0.0)

This table was created by Senior Clinical Analyst Dr. Rui Li.

13.34. ARIA and Intracerebral Hemorrhage > 1 cm by ApoE ε4 Status in the Placebo-Controlled Pool

The following table shows incidence of ARIA and intracerebral hemorrhage > 1 cm by ApoE ε4 status in the placebo-controlled pool.

Table 115. ARIA and Intracerebral Hemorrhage > 1 cm by ApoE ε4 status in the Placebo-controlled Pool¹

	NonCarrier		Heterozygotes		Homozygotes	
	DON N=291 n (%)	PBO N=282 n (%)	DON N=522 n (%)	PBO N=538 n (%)	DON N=168 n (%)	PBO N=174 n (%)
ARIA-E or ARIA-H	70 (24.1)	31 (11.0)	189 (36.2)	63 (11.7)	97 (57.7)	36 (20.7)
ARIA-E	43 (14.8)	2 (0.7)	123 (23.6)	9 (1.7)	69 (41.1)	6 (3.4)
ARIA-H	55 (18.9)	29 (10.3)	157 (30.1)	57 (10.6)	90 (53.6)	33 (19.0)
ARIA-H Microhemorrhages	43 (14.8)	28 (9.9)	126 (24.1)	50 (9.3)	73 (43.5)	27 (15.5)
ARIA-H Superficial Siderosis	24 (8.2)	2 (0.7)	77 (14.8)	11 (2.0)	46 (27.4)	13 (7.5)
Intracerebral hemorrhage > 1 cm ²	1 (0.3)	0	3 (0.6)	1 (0.2)	0	0

¹The incidence of ARIA is based on analyses using the MRI dataset provided by Senior Clinical Analyst Dr. Rui Li. The incidence of intracerebral hemorrhage > 1 cm is based on analyses using the combined adverse event, MRI datasets, and a review of narratives performed by this reviewer.

²One placebo-treated subject with intracerebral hemorrhage > 1 cm had unknown ApoE genotype status (15T-MC-AACI- (b) (6)).

13.35. Serious ARIA and Intracerebral Hemorrhage > 1 cm, Symptomatic ARIA, Treatment Discontinuations and Treatment Interruptions due to ARIA and Intracerebral Hemorrhage > 1 cm by ApoE ε4 status

The following table shows the incidence of serious ARIA and intracerebral hemorrhage, symptomatic ARIA, treatment discontinuations and treatment interruptions due to ARIA and intracerebral hemorrhage > 1 cm by ApoE ε4 status in the placebo-controlled pool.

Table 116. Serious ARIA and Intracerebral Hemorrhage > 1 cm, Symptomatic ARIA, Treatment Discontinuations and Treatment Interruptions due to ARIA and Intracerebral Hemorrhage > 1 cm by ApoE ε4 status in the Placebo-controlled Pool.

Events	Donanemab N=984		
	Noncarriers N=291 n (%)	Heterozygotes N=522 n (%)	Homozygotes N=168 n (%)
ARIA-E			
Serious	1 (0.3)	9 (1.7)	5 (3)
Treatment Discontinuations	2 (0.7)	6 (1.1)	3 (1.8)
Treatment Interruptions	27 (9.3)	78 (14.9)	44 (26.2)
Symptomatic ¹	12 (4.1)	32 (6.1)	13 (7.7)
ARIA-H			
Serious	1 (0.3)	1 (0.2)	2 (1.2)
Treatment Discontinuations	2 (0.7)	2 (0.4)	3 (1.8)
Treatment Interruptions	14 (4.8)	62 (11.9)	41 (24.4)
Intracerebral Hemorrhage > 1 cm ²			
Serious	0	1 (0.2)	0
Treatment Discontinuations	0	2 (0.4)	0
Treatment Interruptions	0	1 (0.2)	0

This reviewer created this table using the 90-Day Safety IDB ADAE dataset, TEPCLDFL, APERIODC= First treatment period. For serious: AESER = Y. For treatment status: AEACN = treatment withdrawn or treatment disrupted.

¹This reviewer created this using the 90-Day Safety IDB ADCE dataset, TEPCLDFL=Y.

²Subject IST-MC-AACI- (b) (6) a noncarrier for ApoE ε4, with events of hemorrhagic stroke and hematoma is not included in the table above as neither event was recorded as an adverse event.

The following tables show serious ARIA and intracerebral hemorrhage > 1 cm, treatment interruptions and treatment discontinuations due to ARIA and intracerebral hemorrhage > 1 cm, and symptomatic ARIA-E by ApoE ε4 status with placebo arms included in the placebo-controlled period of AACI and the placebo-controlled pool.

Table 117. Serious ARIA and Intracerebral Hemorrhage > 1 cm by ApoE ϵ 4 Status in the Placebo-controlled Period of AACI.

	NonCarrier		Heterozygotes		Homozygotes	
	DON N=255 n (%)	PBO N=250 n (%)	DON N=452 n (%)	PBO N=474 n (%)	DON N=143 n (%)	PBO N=146 n (%)
ARIA	2 (0.8)	0	8 (1.8)	0	4 (2.8)	0
ARIA-E	1 (0.4)	0	8 (1.8)	0	4 (2.8)	0
ARIA-H	1 (0.4)	0	1 (0.2)	0	2 (1.4)	0
ARIA-H Microhemorrhage	1 (0.4)	0	1 (0.2)	0	2 (1.4)	0
ARIA-H Superficial siderosis	0	0	0	0	0	0
Intracerebral hemorrhage > 1 cm ¹	0	0	1 (0.2)	0	0	0

This reviewer created this table. For ARIA events: 90-Day Safety IDB ADAE dataset, AESER=Y, TEPCDLFL, APERIODC=First treatment period, STUDYID = AACI. For intracerebral hemorrhage > 1 cm events: the combined MRI dataset and the ADAE datasets were used.

¹Donanemab-treated subject IST-MC-AACI- (b) (6) a noncarrier for ApoE ϵ 4, with hemorrhagic stroke and hematoma is not included in the table above as neither event was recorded as an adverse event. Placebo-treated subject IST-MC-AACI- (b) (6) with hemorrhagic stroke is not included in the table as ApoE ϵ 4 status was unknown.

Table 118. Serious ARIA and Intracerebral Hemorrhage > 1 cm by ApoE ϵ 4 Status in the Placebo-controlled Pool.

	NonCarrier		Heterozygotes		Homozygotes	
	DON N=291 n (%)	PBO N=282 n (%)	DON N=522 n (%)	PBO N=538 n (%)	DON N=168 n (%)	PBO N=174 n (%)
ARIA	2 (0.7)	0	9 (1.7)	0	5 (3)	0
ARIA-E	1 (0.3)	0	9 (1.7)	0	5 (3)	0
ARIA-H	1 (0.3)	0	1 (0.2)	0	2 (1.2)	0
ARIA-H Microhemorrhage	1 (0.3)	0	1 (0.2)	0	2 (1.2)	0
ARIA-H Superficial siderosis	0	0	0	0	0	0
Intracerebral Hemorrhage > 1 cm ¹	0	0	1 (0.2)	0	0	0

This reviewer created this table. For ARIA events: 90-Day Safety IDB ADAE dataset, AESER=Y, TEPCDLFL, APERIODC=First treatment period. For intracerebral hemorrhage > 1 cm events: the combined MRI dataset and the ADAE datasets were used.

¹Donanemab-treated subject IST-MC-AACI- (b) (6) a noncarrier for ApoE ϵ 4, with hemorrhagic stroke and hematoma is not included in the table above as neither event was recorded as an adverse event. Placebo-treated

subject IST-MC-AACI- (b) (6) with hemorrhagic stroke is not included in the table as ApoE ε4 status was unknown.

Table 119. ARIA and Intracerebral Hemorrhage > 1 cm Reported to Lead to Treatment Discontinuation by ApoE ε4 Status in the Placebo-controlled Period of AACI

	NonCarrier		Heterozygotes		Homozygotes	
	DON N=255 n (%)	PBO N=250 n (%)	DON N=452 n (%)	PBO N=474 n (%)	DON N=143 n (%)	PBO N=146 n (%)
ARIA	5 (2)	0	14 (3.1)	1 (0.2)	10 (7)	4 (2.7)
ARIA-E	3 (1.2)	0	10 (2.2)	1 (0.2)	8 (5.6)	2 (1.4)
ARIA-H	2 (0.8)	0	4 (0.9)	0	2 (1.4)	2 (1.4)
ARIA-H Microhemorrhage	2 (0.8)	0	3 (0.7)	0	1 (0.7)	2 (1.4)
ARIA-H Superficial siderosis	0	0	1 (0.2)	0	1 (0.7)	0
Intracerebral Hemorrhage > 1 cm ¹	0	0	2 (0.4)	0	0	0

This reviewer created this table. For ARIA events: 90-Day Safety IDB ADAE dataset, AEACN = treatment withdrawn, TEPCDLFL, APERIODC= First treatment period, STUDYID = AACI. For intracerebral hemorrhage > 1 cm events: the combined MRI dataset and the ADAE datasets were used.

¹Donanemab-treated subject IST-MC-AACI- (b) (6) a noncarrier for ApoE ε4, with hemorrhagic stroke and hematoma is not included in the table above as neither event was recorded as an adverse event. Placebo-treated subject IST-MC-AACI- (b) (6) with hemorrhagic stroke is not included in the table as ApoE ε4 status was unknown.

Table 120. ARIA and Intracerebral Hemorrhage > 1 cm Reported to Lead to Treatment Discontinuation by ApoE ε4 Status in the Placebo-controlled Pool.

	NonCarrier		Heterozygotes		Homozygotes	
	DON N=291 n (%)	PBO N=282 n (%)	DON N=522 n (%)	PBO N=538 n (%)	DON N=168 n (%)	PBO N=174 n (%)
ARIA	4 (1.4)	0	8 (1.5)	1 (0.2)	6 (3.6)	2 (1.1)
ARIA-E	2 (0.7)	0	6 (1.1)	1 (0.2)	3 (1.8)	2 (1.1)
ARIA-H	2 (0.7)	0	2 (0.4)	0	3 (1.8)	0
ARIA-H Microhemorrhage	2 (0.7)	0	1 (0.2)	0	2 (1.2)	0
ARIA-H Superficial siderosis	0	0	1 (0.2)	0	1 (0.6)	0
Intracranial Hemorrhage EMQ/FMQ	2 (0.7)	1 (0.4)	0	0	2 (1.2)	0

	NonCarrier		Heterozygotes		Homozygotes	
	DON N=291 n (%)	PBO N=282 n (%)	DON N=522 n (%)	PBO N=538 n (%)	DON N=168 n (%)	PBO N=174 n (%)
Intracerebral Hemorrhage > 1 cm ¹	0	0	2 (0.4)	0	0	0

This reviewer created this table. For ARIA events: 90-Day Safety IDB ADAE dataset, AEACN = treatment withdrawn, TEPCLDLFL, APERIODC= First treatment period. For intracerebral hemorrhage > 1 cm events: the combined MRI dataset and the ADAE datasets were used.

¹Donanemab-treated subject I5T-MC-AACI- (b) (6), a noncarrier for ApoE ε4, with hemorrhagic stroke and hematoma is not included in the table above as neither event was recorded as an adverse event. Placebo-treated subject I5T-MC-AACI- (b) (6) with hemorrhagic stroke is not included in the table as ApoE ε4 status was unknown.

Table 121. ARIA and Intracerebral Hemorrhage > 1 cm Reported to Lead to Treatment Interruption by ApoE ε4 Status in the Placebo-controlled Period of AACI.

	NonCarrier		Heterozygotes		Homozygotes	
	DON N=255 n (%)	PBO N=250 n (%)	DON N=452 n (%)	PBO N=474 n (%)	DON N=143 n (%)	PBO N=146 n (%)
ARIA	33 (12.9)	9 (3.6)	101 (22.3)	22 (4.6)	53 (37.1)	11 (7.5)
ARIA-E	26 (10.2)	1 (0.4)	74 (16.4)	5 (1.1)	43 (30.1)	1 (0.7)
ARIA-H	14 (5.5)	8 (3.2)	61 (13.5)	17 (3.6)	41 (28.7)	10 (6.8)
ARIA-H Microhemorrhage	13 (5.1)	7 (2.8)	52 (11.5)	16 (3.4)	37 (25.9)	8 (5.5)
ARIA-H Superficial siderosis	2 (0.8)	1 (0.4)	18 (4)	1 (0.2)	8 (5.6)	2 (1.4)
Intracerebral Hemorrhage > 1 cm ¹	0	0	1 (0.2)	1 (0.2)	0	0

This reviewer created this table. For ARIA events: 90-Day Safety IDB ADAE dataset, AEACN = treatment interrupted, TEPCLDLFL, APERIODC= First treatment period, STUDYID = AACI. For intracerebral hemorrhage > 1 cm events: the combined MRI dataset and the ADAE datasets were used.

¹Donanemab-treated subject I5T-MC-AACI- (b) (6), a noncarrier for ApoE ε4, with hemorrhagic stroke and hematoma is not included in the table above as neither event was recorded as an adverse event. Placebo-treated subject I5T-MC-AACI- (b) (6) with hemorrhagic stroke is not included in the table as ApoE ε4 status was unknown.

Table 122. ARIA and Intracerebral Hemorrhage > 1 cm Reported to Lead to Treatment Interruption by ApoE ϵ 4 Status in the Placebo-controlled Pool.

	NonCarrier		Heterozygotes		Homozygotes	
	DON N=291 n (%)	PBO N=282 n (%)	DON N=522 n (%)	PBO N=538 n (%)	DON N=168 n (%)	PBO N=174 n (%)
ARIA	34 (11.7)	9 (3.2)	105 (20.1)	22 (4.1)	54 (32.1)	11 (6.3)
ARIA-E	27 (9.3)	1 (0.4)	78 (14.9)	5 (0.9)	44 (26.2)	1 (0.6)
ARIA-H	14 (4.8)	8 (2.8)	62 (11.9)	17 (3.2)	41 (24.4)	10 (5.7)
ARIA-H Microhemorrhage	13 (4.5)	7 (2.5)	53 (10.2)	16 (3)	37 (22)	8 (4.6)
ARIA-H Superficial siderosis	2 (0.7)	1 (0.4)	19 (3.6)	1 (0.2)	8 (4.8)	2 (1.1)
Intracerebral Hemorrhage > 1 cm ¹	0	0	1 (0.2)	1 (0.2)	0	0

This reviewer created this table. For ARIA events: 90-Day Safety IDB ADAE dataset, AEACN = treatment interrupted, TEPCDLFL, APERIODC= First treatment period. For intracerebral hemorrhage > 1 cm events: the combined MRI dataset and the ADAE datasets were used.

¹Donanemab-treated subject IST-MC-AACI- (b) (6), a noncarrier for ApoE ϵ 4, with hemorrhagic stroke and hematoma is not included in the table above as neither event was recorded as an adverse event. Placebo-treated subject IST-MC-AACI- (b) (6) with hemorrhagic stroke is not included in the table as ApoE ϵ 4 status was unknown.

Table 123. Symptomatic ARIA-E by ApoE ϵ 4 Status in the Placebo-controlled Period of AACI

	NonCarrier		Heterozygotes		Homozygotes	
	DON N=255 n (%)	PBO N=250 n (%)	DON N=452 n (%)	PBO N=474 n (%)	DON N=143 n (%)	PBO N=146 n (%)
Symptomatic ARIA-E	10 (3.9)	0	30 (6.6)	0	12 (8.4)	0

This reviewer created this table using the 90-Day Safety IDB ADCE dataset, TEPCDLFL, STUDYID = AACI.

Table 124. Symptomatic ARIA-E by ApoE ϵ 4 Status in the Placebo-controlled Pool

	NonCarrier		Heterozygotes		Homozygotes	
	DON N=291 n (%)	PBO N=282 n (%)	DON N=522 n (%)	PBO N=538 n (%)	DON N=168 n (%)	PBO N=174 n (%)
Symptomatic ARIA-E	12 (4.1)	0	32 (6.1)	0	13 (7.7)	1 (0.6)

This reviewer created this table using the 90-Day Safety IDB ADCE dataset, TEPCDLFL.

13.36. Incidence of ARIA-E by Doses Received in ApoE ϵ 4 Carriers (MRI dataset)

The following analyses are based on data from the MRI dataset.

Compared to all subjects within the donanemab arm, homozygous ApoE ϵ 4 carriers had similar incidences of developing ARIA-E within the first three and first six doses in the placebo-controlled period of AACI (differences no greater than 2%). ARIA-E was noted to occur as late as after the 13th dose in homozygous carriers in the placebo-controlled period of AACI.

Approximately 59% of donanemab-treated subjects homozygous for ApoE ϵ 4 had developed ARIA-E within the first three doses of donanemab and 88% of subjects within the first six doses.

The following table shows the number of doses prior to ARIA-E in donanemab-treated subjects homozygous for ApoE ϵ 4 in the placebo-controlled period of AACI.

Table 125. Number of Doses Prior to ARIA-E in Donanemab-Treated Subjects Homozygous for ApoE ϵ 4 in the Placebo-controlled Period of AACI (MRI dataset)

Number of Dose Prior ARIA-E	First ARIA-E Subject Numbers	Cumulative First ARIA-E Subject Numbers N(%)
1	4	4 (6.9)
2	2	6 (10.3)
3	28	34 (58.6)
5	3	37 (63.8)
6	14	51 (87.9)
7	3	54 (93.1)
13	4	58 (100)

This table was created by Senior Clinical Analyst Dr. Rui Li.

Similar findings were observed for the placebo-controlled pool for developing ARIA-E within the first three and six doses for donanemab-treated subjects homozygous for ApoE ϵ 4 compared to the placebo-controlled period of AACI (difference no greater than 1%).

The following table shows the number of doses prior to ARIA-E in donanemab-treated subjects homozygous for ApoE ϵ 4 in the placebo-controlled pool.

Table 126. Number of Doses Prior to ARIA-E in Donanemab-Treated Subjects Homozygous for ApoE ϵ 4 in the Placebo-Controlled Pool (MRI dataset)

Number of Dose Prior to ARIA-E	First ARIA-E Subject Numbers	Cumulative First ARIA-E Subject Numbers N(%)
1	4	4 (5.8)
2	4	8 (11.6)
3	33	41 (59.4)
5	4	45 (65.2)
6	15	60 (87.0)
7	4	64 (92.8)

Clinical Review
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 BLA 761248
 Kisunla/donanemab

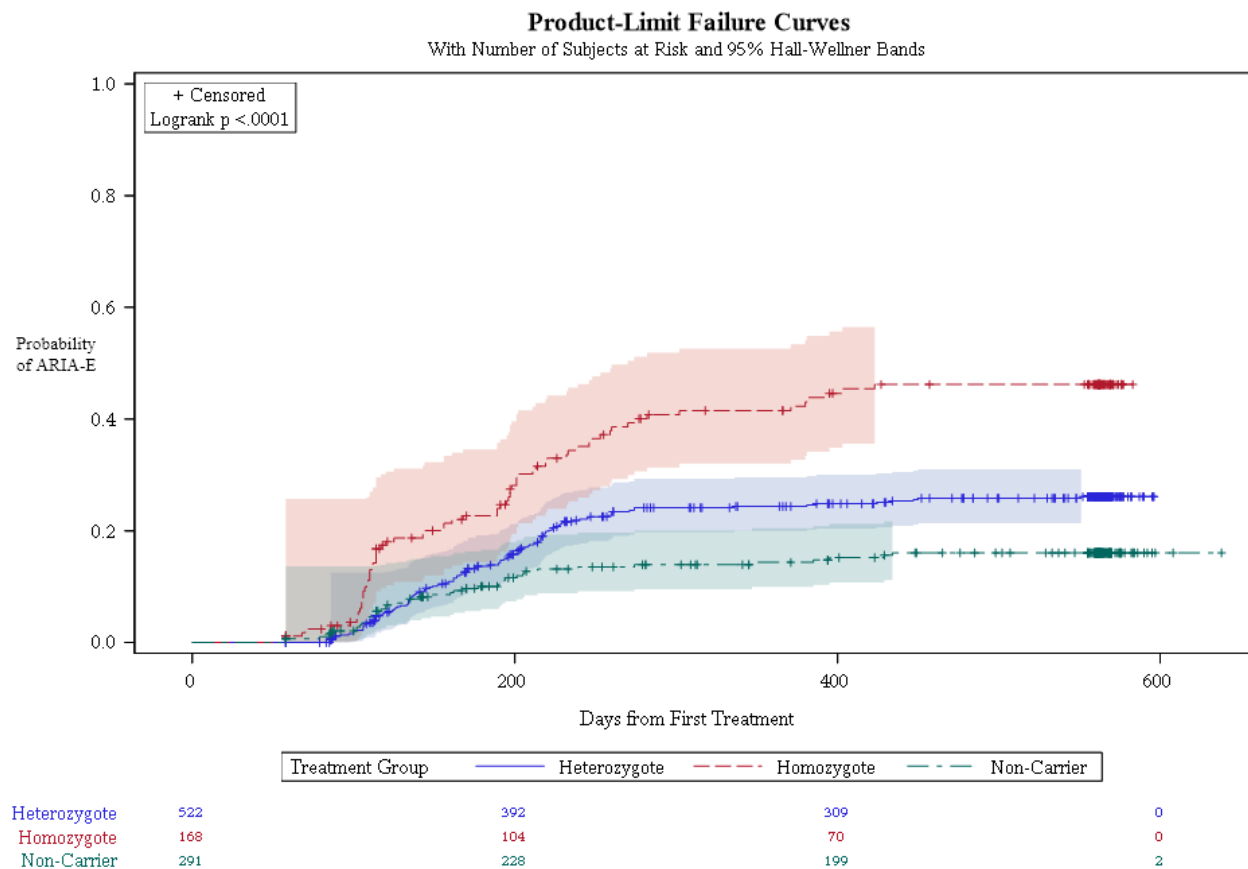
Number of Dose Prior to ARIA-E	First ARIA-E Subject Numbers	Cumulative First ARIA-E Subject Numbers N(%)
10	1	65 (94.2)
13	4	69 (100)

This table was created by Senior Clinical Analyst Dr. Rui Li.

13.37. Time to First ARIA-E Event for the Placebo-controlled Pool (MRI Dataset)

In the placebo-controlled pool, among donanemab-treated subjects homozygous for ApoE $\epsilon 4$, the majority of first ARIA-E events had occurred by 400 days from first treatment. The following plot shows time to first ARIA-E event by ApoE $\epsilon 4$ status among donanemab-treated subjects in the placebo-controlled pool.

Figure 7. Probability of First ARIA-E Event for the Placebo-controlled Pool (MRI dataset)



The above figure was created by Senior Clinical Analyst Dr. Rui Li.

13.38. Incidence of ARIA-H and Intracerebral Hemorrhage > 1 cm with Antithrombotic Use in the Placebo-controlled Pool

The following table shows the incidence of ARIA-H and intracerebral hemorrhage > 1 cm by antithrombotic use in the placebo-controlled pool.

Table 127. Incidence of Subjects with ARIA-H or Intracerebral Hemorrhage > 1 cm by Antithrombotic Use in the Placebo-controlled Pool

Event ¹	DON		Placebo	
	AT use N=411 n (%)	No AT Use N=573 n (%)	AT use N=428 n (%)	No AT Use N=571 n (%)
ARIA-H	124 (30.2)	168 (29.3)	52 (12.1)	66 (11.6)
Intracerebral Hemorrhage > 1 cm	2 (0.5)	2 (0.3)	0	2 (0.4)

AT: Antithrombotic

¹Subjects are included if they had an event 1) while on an antithrombotic or 2) used an antithrombotic within 30 days prior to the event.

The following table shows the incidence of ARIA-H and intracerebral hemorrhage > 1 cm by antithrombotic class use in the placebo-controlled pool.

Table 128. Incidence of Subjects with ARIA-H or Intracerebral Hemorrhage > 1 cm by Antithrombotic Class Use in the Placebo-controlled Pool¹

Event ²	DON			Placebo		
	ASA ≤ 81 mg N=311 n (%)	ASA > 81 or APT or ASA and APT N=80 n (%)	AC N=95 n (%)	ASA ≤ 81 mg N=313 n (%)	ASA > 81 or APT or ASA and APT N=74 n (%)	AC N=100 n (%)
ARIA-H	98 (31.5)	19 (23.8)	22 (23.2)	40 (12.8)	11 (14.9)	12 (12.0)
Intracerebral Hemorrhage > 1 cm	0	2 (2.5)	0	0	0	0

AC: Anticoagulant, APT: Antiplatelet therapy, ASA: Aspirin.

¹A subject can contribute to multiple antithrombotic classes.

²Subjects are included if they had an event 1) while on an antithrombotic or 2) used an antithrombotic within 30 days prior to the event.

13.39. Subjects with Seizure, Seizure with ARIA-E, and Seizure with Intracerebral Hemorrhage in the Placebo-Controlled Pool and the All-Donanemab Pool

The following table shows the incidence of seizure, seizure with ARIA-E, and seizure with intracerebral hemorrhage in the placebo-controlled pool.

Table 129. Incidence of Seizure, Seizure with ARIA-E, and Seizure with Intracerebral Hemorrhage in the Placebo-Controlled Pool

AEs	Donanemab N=984 n (%)	Placebo N=999 n (%)
Seizure	10 (1.0)	3 (0.3)
Serious seizure ¹	3 (0.3)	1 (0.1)
Seizure with ARIA ¹	5 (0.5)	0
Seizure with intracerebral hemorrhage	0	0
Serious seizure with intracerebral hemorrhage	0	0
Seizure without either ARIA or intracerebral hemorrhage	5 (0.5)	3 (0.3)
Serious seizure without either ARIA or intracerebral hemorrhage ¹	2 (0.2)	1 (0.1)

This reviewer created this table using the 90-Day Safety Update ADAE and ADCE datasets.

¹Seizures recorded as symptoms of ARIA (recorded in the ADCE dataset) were not assessed for seriousness.

The following table shows the incidence of seizure, seizure with ARIA-E, and seizure with intracerebral hemorrhage in the all-donanemab pool.

Table 130. Incidence of Seizure, Seizure with ARIA-E, and Seizure with Intracerebral Hemorrhage in the All-Donanemab Pool

AEs	Donanemab N=2802 n (%)
Seizure ²	20 (0.7)
Serious seizure ¹	7 (0.2)
Seizure with ARIA ^{1,2}	7 (0.2)

AEs	Donanemab N=2802 n (%)
Seizure with intracerebral hemorrhage	1 (<0.5)
Serious seizure with intracerebral hemorrhage	1 (<0.5)
Seizure without either ARIA or intracerebral hemorrhage	12 (0.4)
Serious seizure without either ARIA or intracerebral hemorrhage ¹	5 (0.2)

This reviewer created this table using the 90-Day Safety Update ADAE and ADCE datasets.

¹Seizures recorded as symptoms of ARIA (recorded in the ADCE dataset) were not assessed for seriousness.

²This includes IST-MC-AACI- (b) (6) who did not have seizure recorded in either the adverse event or the symptomatic ARIA-E datasets.

SAEs of Seizure and Subdural Hematoma, subarachnoid bleed, IST-MC-AACI- (b) (6)

A 68-year-old female with medical history of sleep apnea, headache, APOE genotype ε3ε4 who developed the SAE of seizure 75 days after the first dose of donanemab and 19 days after the 3rd dose of donanemab (Study Day 57). MRI findings from Study Day 26 showed no microhemorrhages and white matter abnormalities. On Study Day 67, the subject developed worsening headache. On Study Day 69, the subject fell three times while getting off a chairlift while skiing and hit her head in the snow. On Study Day 71, an MRI showed a subarachnoid bleed in the right frontal lobe, new bilateral chronic subdural collections (preferred term subdural hygroma, moderate in severity), and new left frontal area of hemosiderin measuring 4 mm on the right and 3 mm on the left side in the frontal regions. On the same day, and 15 days after the administration of the third dose of donanemab, the subject was diagnosed with the AE of moderate ARIA-H. Four days later, the subject experienced the AE of myoclonic jerks and was hospitalized for the SAE of seizure. The subject was treated with levetiracetam and recovered from the events of myoclonus and seizure on the same day. Study drug was withdrawn due to the event of ARIA-H. The final dose of study drug was on Study Day 57. Forty-nine days after the final dose, the subject experienced the SAE of severe subdural hematoma (worsening right subdural hematoma). A follow up CT scan 8 days later showed bleeding. The subject was hospitalized that day and underwent evacuation of the hematoma the following day. The AEs of headache and ARIA-H were reported as resolving at the time of the data cutoff and the subdural hematoma was considered not resolved.

Reviewer comment: A role for donanemab in the SAE of seizure could not be established because of the concurrent events of subarachnoid bleed and subdural hygroma, which were likely contributory. A role for donanemab in the events of subarachnoid bleed or subdural hematoma cannot be established because of the preceding events of fall, which were likely contributory.

13.1. ARIA Radiographic Severity by ApoE ϵ 4 Status in the Placebo-controlled Pool (MRI Dataset)

The following analyses are based on data from the MRI dataset.

In the placebo-controlled pool, donanemab-treated subjects homozygous for ApoE ϵ 4 had higher incidences of radiographically severe ARIA, ARIA-E, ARIA-H, ARIA-H Microhemorrhage, and ARIA-H Superficial siderosis compared to heterozygous and non-carriers. Radiographically severe ARIA-E occurred in 4.2% of donanemab-treated subjects homozygous for ApoE ϵ 4 compared to 2.1% of heterozygous carriers and 1.0% of non-carriers. Radiographically severe ARIA-H occurred in 22.0% of donanemab-treated subjects homozygous for ApoE ϵ 4 compared to 8.2% of heterozygous carriers and 3.8% of non-carriers.

The following table shows radiographic severity of ARIA by ApoE ϵ 4 status in the placebo-controlled pool.

Table 131. ARIA Radiographic Severity by ApoE ϵ 4 Status in the Placebo-controlled Pool (MRI dataset).

	NonCarrier		Heterozygotes		Homozygotes	
	DON N=291 n (%)	PBO N=282 n (%)	DON N=522 n (%)	PBO N=538 n (%)	DON N=168 n (%)	PBO N=174 n (%)
Total Subjects with Any ARIA Events						
Mild	35 (12.0)	26 (9.2)	75 (14.4)	55 (10.2)	30 (17.9)	26 (14.9)
Moderate	22 (7.6)	3 (1.1)	68 (13.0)	8 (1.5)	28 (16.7)	9 (5.2)
Severe	13 (4.5)	2 (0.7)	46 (8.8)	0	39 (23.2)	1 (0.6)
Total	70 (24.1)	31 (11.0)	189 (36.2)	63 (11.7)	97 (57.7)	36 (20.7)
ARIA-E						
Mild	13 (4.5)	2 (0.7)	40 (7.7)	8 (1.5)	16 (9.5)	4 (2.3)
Moderate	26 (8.9)	0	72 (13.8)	1 (0.2)	46 (27.4)	2 (1.1)
Severe	3 (1.0)	0	11 (2.1)	0	7 (4.2)	0
Total	43 (14.8)	2 (0.7)	123 (23.6)	9 (1.7)	69 (41.1)	6 (3.4)
ARIA-H						
Mild	39 (13.4)	24 (8.5)	79 (15.1)	50 (9.3)	38 (22.6)	25 (14.4)
Moderate	5 (1.7)	3 (1.1)	35 (6.7)	7 (1.3)	15 (8.9)	7 (4.0)
Severe	11 (3.8)	2 (0.7)	43 (8.2)	0	37 (22.0)	1 (0.6)
Total	55 (18.9)	29 (10.3)	157 (30.1)	57 (10.6)	90 (53.6)	33 (19.0)
ARIA-H, Microhemorrhages						
Mild	39 (13.4)	24 (8.5)	85 (16.3)	44 (8.2)	38 (22.6)	25 (14.4)
Moderate	3 (1.0)	3 (1.1)	22 (4.2)	6 (1.1)	10 (6.0)	2 (1.1)

	NonCarrier		Heterozygotes		Homozygotes	
	DON N=291 n (%)	PBO N=282 n (%)	DON N=522 n (%)	PBO N=538 n (%)	DON N=168 n (%)	PBO N=174 n (%)
Severe	1 (0.3)	1 (0.4)	19 (3.6)	0	25 (14.9)	0
Total	43 (14.8)	28 (9.9)	126 (24.1)	50 (9.3)	73 (43.5)	27 (15.5)
ARIA-H, Superficial Siderosis						
Mild	10 (3.4)	1 (0.4)	29 (5.6)	10 (1.9)	17 (10.1)	7 (4.0)
Moderate	4 (1.4)	0	21 (4.0)	1 (0.2)	11 (6.5)	5 (2.9)
Severe	10 (3.4)	1 (0.4)	27 (5.2)	0	18 (10.7)	1 (0.6)
Total	24 (8.2)	2 (0.7)	77 (14.8)	11 (2.0)	46 (27.4)	13 (7.5)

The reviewer created this table using analyses by Senior Clinical Analyst Dr. Rui Li.

13.2. TEAEs of Infusion Related Reaction in the Placebo-Controlled Pool

The following table shows the incidence of TEAEs of infusion related reactions in the placebo-controlled pool.

Table 132. TEAEs of Infusion Related Reactions in the Placebo-Controlled Pool

Preferred Term	Donanemab N=984 n (%)	Placebo N=999 n (%)
TEAEs	84 (8.5)	4 (0.4)
Serious	3 (0.3)	0
Reported to Lead to Study Withdrawal	24 (2.4)	0
Reported to Lead to Treatment Discontinuation	38 (3.9)	0

This table was created by this reviewer using the 90Day Safety Update ADAE dataset, TEPCLDLFL =Y, APERIODC = First Treatment period, AEDECOD = infusion related reaction, AESER = Y or DISAEFL = Y or AEACN = Drug Withdrawn.

The following table shows the maximum severity of TEAEs of infusion related reactions among subjects who experienced infusion related reactions in the placebo-controlled period of AACI.

Table 133. TEAEs of Infusion Related Reactions by Maximum Severity Among Subjects Who Experienced Infusion Related Reactions in the Placebo-Controlled Period of AACI

Preferred Term	Donanemab N=74 n (%)	Placebo N=4 n (%)
Subjects with TEAEs of Infusion Related Reactions	74 (100)	4 (100)
Mild	42 (56.8)	3 (75.0)
Moderate	29 (39.2)	1 (25.0)
Severe	3 (4.1)	0

This table was created by this reviewer using the 90Day Safety Update ADAE dataset, TEPCDLFL =Y, APERIODC = First Treatment period, AEDECOD = infusion related reaction, ASEV = mild, moderate, or severe, STUDYID = AACI.

The following table shows the maximum severity of TEAEs of infusion related reactions among subjects who experienced infusion related reactions in the placebo-controlled pool.

Table 134. TEAEs of Infusion Related Reactions by Maximum Severity Among Subjects Who Experienced Infusion Related Reactions in the Placebo-Controlled Pool

Preferred Term	Donanemab N=84 n (%)	Placebo N=4 n (%)
Subjects with TEAEs of Infusion related Reactions	84 (100)	4 (100)
Mild	45 (53.6)	3 (75)
Moderate	34 (40.5)	1 (25)
Severe	5 (6.0)	0

This table was created by this reviewer using the 90Day Safety Update ADAE dataset, TEPCDLFL =Y, APERIODC = First Treatment period, AEDECOD = infusion related reaction, ASEV = mild, moderate, or severe.

The following table shows the timing of symptoms associated with infusion related reactions in the placebo-controlled period of AACI.

Table 135. Timing of Symptoms of Infusion Related Reaction in the Placebo-Controlled Period of AACI

Timing of Symptoms	Donanemab N=853 n (%)	Placebo N=874 n (%)
Subjects Reporting Symptoms ¹	73 (8.6)	4 (0.5)
During drug administration	57 (6.7)	1 (0.1)

Timing of Symptoms	Donanemab N=853 n (%)	Placebo N=874 n (%)
Within 30 minutes of end of study drug administration	12 (1.4)	1 (0.1)
>30 minutes and up to 6 hours from end of study drug administration	8 (0.9)	1 (0.1)
>6 hours and up to 24 hours from end of study drug administration	6 (0.7)	0
>24 hours and up to 14 days from study drug administration	2 (0.2)	2 (0.2)

The reviewer created this table using the IDB ADAEFA dataset, TEPCDLFL = Y, AEDECOD = Infusion Related Reaction, STUDYID = AACI.

¹Timing of symptoms of infusion related reactions were recorded on a separate form for infusion related reactions. Not all subjects with infusion related reactions recorded symptoms.

The following table shows the timing of symptoms associated infusion related reactions in the placebo-controlled pool.

Table 136. Timing of Symptoms of Infusion Related Reaction in the Placebo-Controlled Pool

Timing of Symptoms	Donanemab N=984 n (%)	Placebo N=999 n (%)
Subjects Reporting Symptoms ¹	83 (8.4)	4 (0.4)
During drug administration	64 (6.5)	1 (0.1)
Within 30 minutes of end of study drug administration	14 (1.4)	1 (0.1)
>30 minutes and up to 6 hours from end of study drug administration	10 (1)	1 (0.1)
>6 hours and up to 24 hours from end of study drug administration	6 (0.6)	0
>24 hours and up to 14 days from study drug administration	2 (0.2)	2 (0.2)

The reviewer created this table using the 90Day Safety Update ADAEFA, TEPCDLFL = Y, AEDECOD = Infusion Related Reaction.

¹Timing of symptoms of infusion related reactions were recorded on a separate form for infusion related reactions. Not all subjects with infusion related reactions recorded symptoms.

The following table shows the number of donanemab doses received prior to the first event of infusion related reaction in the placebo-controlled period of AACI.

Clinical Review
Natalie Branagan, MD
BLA 761248
Kisunla/donanemab

Table 137. First Infusion Related Reaction by Donanemab Dose Number in the Placebo-Controlled Period of AACI.

# of Doses Received	# of Subjects	Cumulative # of Subjects	Cumulative %
1	7	7	9.5
2	22	29	39.2
3	7	36	48.6
4	16	52	70.3
5	7	59	79.7
6	6	65	87.8
7	4	69	93.2
13	3	72	97.3
14	1	73	98.6
15	1	74	100.0

The reviewer created this table using 90Day Safety Update ADEX and the 90Day Safety Update ADAE.

The following figure shows the number of donanemab doses received prior to the first event of infusion related reaction in the placebo-controlled pool.

Figure 8. Number of Donanemab Doses Received Prior to First Event of Infusion Related Reaction in the Placebo-Controlled Pool

# of Donanemab Infusions Received Before First IRR (PT) *a	# of Participants	Cumulative # of Participants	Cumulative % of Total Participants Experiencing IRR (PT) *a
1	7	7	8.33%
2	24	31	36.90%
3	7	38	45.24%
4	21	59	70.24%
5	10	69	82.14%
6	6	75	89.29%
7	4	79	94.05%
8	0	79	94.05%
9	0	79	94.05%
10	0	79	94.05%
11	0	79	94.05%
12	0	79	94.05%
13	3	82	97.62%
14	1	83	98.81%
15	1	84	100.00%

This table includes treatment-emergent events that occurred up to last treatment + 57 days.

*a Events included are those with Preferred Term of 'Infusion related reaction'.

Data submitted by the Applicant in a response dated January 9, 2024, to an information request dated January 4, 2024.

The following table shows the incidence of most frequent symptoms reported with infusion related reaction among donanemab-treated subjects compared to placebo in the placebo-controlled period of AACI.

Table 138. Symptoms of Infusion Related Reactions With Incidence of at Least 1% Higher in Donanemab Arm compared to Placebo in the Placebo-controlled Period of AACI

Preferred Term	Donanemab N=853 n (%)	Placebo N=874 n (%)
Chills	29 (3.4)	0
Erythema	29 (3.4)	1 (0.1)
Nausea/Vomiting	28 (3.3)	0
Difficulty Breathing/Dyspnea ¹	15 (1.8)	0
Sweating	14 (1.6)	0
Elevated Blood Pressure	13 (1.5)	0
Headache	12 (1.4)	0
Chest Pain ²	11 (1.3)	0
Low Blood Pressure	9 (1.1)	0

This table was created by this reviewer using the 90Day Safety Update ADAEFA, TEPCDLFL=Y, AEDECOD = Infusion Related Reaction, STUDYID = AACI.

¹Includes hyperventilation.

²Includes chest pressure, chest heaviness, and tight chest.

The following table shows the incidence of infusion related reactions in subjects who received medication pretreatment upon rechallenge compared to subjects who did not receive medication pretreatment upon rechallenge in the all-donanemab pool at the time of the resubmission and at the time of the 90-Day Safety Update of the resubmission.

Figure 9. Incidence of Infusion Related Reactions at Rechallenge and Pretreatment Medication Use in the All-Donanemab Pool

	90-Day RSUR All Dona Donanemab (N = 2802) n/N (%)	RSUR All Dona Donanemab {N = 2727} n/N {%}
Participants with IRR	266	252
Participants with rechallenge infusion	181/266 (68.1%)	164/252 {65.1%}
Prophylaxis medication for rechallenge	42/181 (23.2%)	38/164 {23.2%}
IRR upon rechallenge infusion	16/42 (38.1%)	15/38 {39.5%}
No IRR upon rechallenge infusion	26/42 (61.9%)	23/38 {60.5%}
No prophylaxis medication for rechallenge	139/181 (76.8%)	126/164 {76.8%}
IRR upon rechallenge infusion	57/139 (41.0%)	53/126 {42.1%}
No IRR upon rechallenge infusion	82/139 (59.0%)	73/126 {57.9%}

Abbreviations: IRR = infusion-related reaction; n = number of participants within each specific category;

N = number of treated participants; RSUR = Resubmission Safety Update Report.

The above figure was taken from the Applicant's 90-Day Safety Update RSUR dated September 9, 2023 for the donanemab resubmission.

The following table shows the incidence of infusion related reactions in subjects who had infusions slowed upon rechallenge compared to subjects who did not have infusions slowed upon rechallenge in the all-donanemab pool at the time of the resubmission and at the time of the 90-Day Safety Update of the resubmission.

Figure 10. Incidence of Infusion Related Reactions at Rechallenge and Slowing of Infusion in the All-Donanemab Pool

	90-Day RSUR All Dona Donanemab (N = 2802) n/N (%)	RSUR All Dona Donanemab (N = 2727) n/N {%}
Participants with first IRR	266	252
Participants with rechallenge infusion	181/266 (68.1%)	164/252 {65.1%}
Slowed infusion for rechallenge ^a	77/181 (42.5%)	72/164 {43.9%}
IRR upon rechallenge infusion	31/77 (40.3%)	30/72 {41.7%}
No IRR upon rechallenge infusion	46/77 (59.7%)	42/72 {58.3%}
No slowed infusion for rechallenge	104/181 (57.5%)	92/164 {56.1%}
IRR upon rechallenge infusion	42/104 (40.4%)	38/92 {41.3%}
No IRR upon rechallenge infusion	62/104 (59.6%)	54/92 {58.7%}

Abbreviations: IRR = infusion-related reaction; n = number of participants within each specific category;

N = number of treated participants.

^a A slowed infusion is defined as an infusion of 45 minutes or longer.

The above figure was taken from the Applicant's 90-Day Safety Update RSUR dated September 9, 2023 for the donanemab resubmission.

13.3. TEAEs of Dermatitis/Eczema, Allergic Rhinitis, and Rash

The following table shows TEAEs of dermatitis/eczema, allergic rhinitis, and rash in the placebo-controlled period of AACI.

Table 139. TEAEs of Dermatitis/Eczema, Allergic Rhinitis, and Rash in the Placebo-controlled Period of AACI.

Preferred Term	Donanemab N=853 n (%)	Placebo N=874 n (%)
Dermatitis/Eczema ¹	15 (1.8)	16 (1.8)
Allergic Rhinitis	3 (0.3)	5 (0.5)
Rash ²	20 (2.3)	18 (2.1)

¹The grouping includes dermatitis allergic, dermatitis atopic, dermatitis bullous, dermatitis contact, and eczema.

²The grouping includes rash erythematous, rash macular, rash maculo-papular, rash pruritic.

The following table shows TEAEs of dermatitis/eczema, allergic rhinitis, and rash in the placebo-controlled pool.

Table 140. TEAEs of Dermatitis/Eczema, Allergic Rhinitis, and Rash in the Placebo-controlled Pool.

Preferred Term	Donanemab N=984 n (%)	Placebo N=999 n (%)
Dermatitis/Eczema ¹	18 (1.8)	19 (1.9)
Allergic Rhinitis	3 (0.3)	5 (0.5)
Rash ²	20 (2.0)	25 (2.5)

¹The grouping includes dermatitis allergic, dermatitis atopic, dermatitis bullous, dermatitis contact, and eczema.

²The grouping includes rash erythematous, rash macular, rash maculo-papular, rash pruritic.

13.4. TEAEs of Hypersensitivity (includes Anaphylaxis and Grouped Terms of Hypersensitivity and Angioedema)

The following table shows TEAEs of hypersensitivity (includes anaphylaxis and grouped terms of hypersensitivity and angioedema) in the placebo-controlled pool.

Table 141. TEAEs of Hypersensitivity (includes Anaphylaxis and Grouped Terms of Hypersensitivity and Angioedema) in the Placebo-Controlled Pool

Preferred Term	Donanemab N=984 n (%)	Placebo N=999 n (%)
Other TEAEs of SMQ of Hypersensitivity (excluding IRRs, dermatitis, eczema, allergic rhinitis, or rash)	27 (2.7)	10 (1.0)
Grouped Terms Related to Hypersensitivity ¹	12 (1.2)	3 (0.3)
Grouped Terms Related to Angioedema	11 (1.1)	7 (0.7)
Angioedema	2 (0.2)	2 (0.2)
Eye edema	1 (0.1)	0
Eyelid edema	2 (0.2)	0
Face edema	2 (0.2)	1 (0.1)
Lip swelling	1 (0.1)	0
Mouth swelling	0	1 (0.1)
Pharyngeal swelling	0	1 (0.1)
Swelling face	0	1 (0.1)
Urticaria	4 (0.4)	1 (0.1)
Urticaria papular	0	1 (0.1)
Anaphylactic reaction	3 (0.3)	0
Drug Eruption	1 (0.1)	0

The reviewer created this table using the 90Day Safety Update ADAE, TEPCDLFL, APERIODC = First Treatment period, SMQ13SC = Narrow.

¹Infusion related hypersensitivity reaction and infusion site hypersensitivity

13.5. Outcomes of TEAEs Excluding Infusion Related Reactions Belonging to the Hypersensitivity SMQ

The following table shows outcomes of TEAEs belonging to the Hypersensitivity SMQ other than infusion related reactions in the placebo-controlled period of AACI.

Table 142. TEAEs Excluding Infusion Related Reactions Belonging to the Hypersensitivity SMQ in the Placebo-Controlled Period of AACI

Preferred Term	Donanemab N=853 n (%)	Placebo N=874 n (%)
TEAEs Belonging to the Hypersensitivity SMQ Excluding Infusion Related Reaction	62 (7.3)	44 (5.0)
Serious	2 (0.2)	1 (0.1)
Reported to Lead to Study Withdrawal	3 (0.4)	0

Preferred Term	Donanemab N=853 n (%)	Placebo N=874 n (%)
Reported to Lead to Treatment Discontinuation	9 (1.1)	0

This table was created by this reviewer using the 90Day Safety Update ADAE dataset, TEPCDLFL =Y, APERIODC = First Treatment period, SMQ13SC = narrow, AEDECOD= inverse of infusion related reaction, AESER = Y or DISAEFL = Y or AEACN = Drug Withdrawn, STUDYID = AACI.

The following table shows the incidence of TEAEs excluding infusion related reactions belonging to the Hypersensitivity SMQ in the placebo-controlled pool.

Table 143. TEAEs Excluding Infusion Related Reactions Belonging to the Hypersensitivity SMQ in the Placebo-Controlled Pool

Preferred Term	Donanemab N=984 n (%)	Placebo N=999 n (%)
TEAEs	66 (6.7)	58 (5.8)
Serious	2 (0.2)	1 (0.1)
Reported to Lead to Study Withdrawal	3 (0.4)	0
Reported to Lead to Treatment Discontinuation	9 (1.1)	0

This table was created by this reviewer using the 90Day Safety Update ADAE dataset, TEPCDLFL =Y, APERIODC = First Treatment period, SMQ13SC = narrow, AEDECOD= inverse of infusion related reaction, AESER = Y or DISAEFL = Y or AEACN = Drug Withdrawn.

The following table shows maximum severity of TEAEs excluding infusion related reaction belonging to the Hypersensitivity SMQ in the placebo-controlled period of AACI.

Table 144. TEAEs, Excluding Infusion Related Reaction, Belonging to the Hypersensitivity SMQ by Maximum Severity in the Placebo-Controlled Period of AACI

Preferred Term	Donanemab N=853 n (%)	Placebo N=874 n (%)
TEAEs	62 (7.3)	44 (5.0)
Mild	41 (4.8)	35 (4)
Moderate	18 (2.1)	7 (0.8)
Severe	3 (0.4)	2 (0.2)

This table was created by this reviewer using the 90Day Safety Update ADAE dataset, TEPCDLFL =Y, APERIODC = First Treatment period, SMQ13SC = narrow, AEDECOD = inverse of infusion related reaction, ASEV = mild, moderate, or severe, STUDYID = AACI.

The following table shows maximum severity of TEAEs excluding infusion related reaction belonging to the Hypersensitivity SMQ in the placebo-controlled pool.

Table 145. TEAEs Other than Infusion Related Reactions Belonging to the Hypersensitivity SMQ by Maximum Severity in the Placebo-Controlled Pool

Preferred Term	Donanemab N=984 n (%)	Placebo N=999 n (%)
TEAEs	66 (6.7)	58 (5.8)
Mild	43 (4.4)	46 (4.6)
Moderate	20 (2)	10 (1)
Severe	3 (0.3)	2 (0.2)

This table was created by this reviewer using the 90Day Safety Update ADAE dataset, TEPCDLFL =Y, APERIODC = First Treatment period, SMQ13SC = narrow, AEDECOD = inverse of infusion related reaction, ASEV = mild, moderate, or severe.

The following table shows the incidence of TEAEs, excluding infusion related reaction, belonging to the Hypersensitivity SMQ occurring within 24 hours of an infusion in the placebo-controlled pool.

Table 146. Incidence of TEAEs, Excluding Infusion Related Reactions, Belonging to the Hypersensitivity SMQ Within 24 Hours of an Infusion in the Placebo-controlled Pool.

TEAEs	Donanemab N=984 n (%)	Placebo N=999 n (%)
TEAEs	62 (7.3)	44 (5.0)
TEAEs within 24 Hours	20 (2)	8 (0.8)

This table was created by this reviewer using the 90Day Safety Update ADAE dataset, TEPCDLFL =Y, APERIODC = First Treatment period, SMQ13SC = Narrow, AEDECOD = inverse of infusion related reaction, AEDOSEFL =Y.

The following table shows the number of donanemab doses received prior to the first TEAE, excluding infusion related reaction, belonging to the Hypersensitivity SMQ in the placebo-controlled period of AACI.

Table 147. Number of Donanemab Doses Received Prior to First Event of Hypersensitivity Other than Infusion Related Reaction by Donanemab Dose Number in the Placebo-Controlled Period of AACI.

# of Doses Received	# of Subjects	Cumulative # of Subjects	Cumulative %
1	11	11	16.7

# of Doses Received	# of Subjects	Cumulative # of Subjects	Cumulative %
2	11	22	33.3
3	6	28	42.4
4	4	32	48.5
5	6	38	57.6
6	1	39	59.1
7	8	47	71.2
8	3	50	75.8
9	2	52	78.8
10	0	52	78.8
11	1	53	80.3
12	1	54	81.8
13	1	55	83.3
14	4	59	89.4
15	1	60	90.9
16	0	60	90.9
17	1	61	92.4
18	0	61	92.4
19	1	62	93.9

The reviewer created this table using 90Day Safety Update ADEX and the 90Day Safety Update ADAE.

The following table shows the number of donanemab doses received prior to the first TEAE, excluding infusion related reaction, belonging to the Hypersensitivity SMQ in the placebo-controlled pool.

Table 148. Time to First TEAE, excluding Infusion Related Reaction, Belonging to the Hypersensitivity SMQ by Donanemab Dose Number in the Placebo-Controlled Pool.

# of Doses Received	# of Subjects	Cumulative # of Subjects	Cumulative %
1	12	12	18.2
2	11	23	34.8
3	7	30	45.5
4	5	35	53.0
5	6	41	62.1
6	1	42	63.6
7	8	50	75.8
8	3	53	80.3
9	3	56	84.8
10	0	56	84.8
11	1	57	86.4

# of Doses Received	# of Subjects	Cumulative # of Subjects	Cumulative %
12	1	58	87.9
13	1	59	89.4
14	4	63	95.5
15	1	64	97.0
16	0	64	97.0
17	1	65	98.5
18	0	65	98.5
19	1	66	100.0

The reviewer created this table using 90Day Safety Update ADEX and the 90Day Safety Update ADAE.

13.1. TEAEs of Intestinal Obstruction and Intestinal Perforation

The following table shows TEAEs related to intestinal obstruction or intestinal perforation in the placebo-controlled pool.

Table 149. TEAEs Related to the Intestinal Obstruction or Intestinal Perforation in the Placebo-controlled Pool

Preferred Terms and Groups of Preferred Terms	Donanemab N=984 n (%)	Placebo N=999 n (%)
Grouped Terms of Intestinal Obstruction	5 (0.5)	0
Small intestinal obstruction	4 (0.4)	0
Intestinal obstruction	1 (0.1)	0
Grouped Terms of Intestinal Perforation	2 (0.2)	1 (0.1)
Intestinal perforation	1 (0.1)	0
Large intestine perforation	1 (0.1)	0
Small intestinal perforation	0	1 (0.1)

This reviewer created this table using the 90-Day Safety IDB ADAE dataset, TEPCLDFL = Y, APERIODC = First Treatment Period.

13.1. SAEs belonging to the Gastrointestinal Disorder SOC in the Placebo-controlled Pool

The following table shows the incidence of SAEs related to the Gastrointestinal tract in the placebo-controlled pool.

Table 150. SAEs Related to the Gastrointestinal Tract in the Placebo-controlled Pool

Preferred Terms and Groups of Preferred Terms	Donanemab N=984 n (%)	Placebo N=999 n (%)
Grouped Terms Related to Intestinal Obstruction	5 (0.5)	0
Intestinal obstruction	1 (0.1)	0
Small intestinal obstruction	4 (0.4)	0
Grouped Terms Related to Intestinal Perforation	2 (0.2)	1 (0.1)
Intestinal perforation	1 (0.1)	0
Large intestine perforation	1 (0.1)	0
Small intestine perforation	0	1 (0.1)
Grouped Terms Related to Colitis	2 (0.2)	0
Clostridium difficile colitis	1 (0.1)	0
Colitis	1 (0.1)	0
Grouped Terms Related to Hernia	3 (0.3)	1 (0.1)
Femoral hernia strangulated	1 (0.1)	0
Inguinal hernia	2 (0.2)	1 (0.1)
Grouped Terms Related to Pancreatitis	3 (0.3)	2 (0.2)
Pancreatitis acute	2 (0.2)	0
Pancreatitis	1 (0.1)	1 (0.1)
Obstructive pancreatitis	0	1 (0.1)
Gastroenteritis	1 (0.1)	0
Obstruction gastric	1 (0.1)	0
Lower gastrointestinal hemorrhage	0	1 (0.1)
Diarrhea	0	1 (0.1)
Gastritis, Duodenitis	2 (0.2)	4 (0.4)
Duodenitis	1 (0.1)	0
Gastritis erosive	1 (0.1)	0
Esophagitis	1 (0.1)	0
Gastric antral vascular ectasia	0	1 (0.1)
Gastric ulcer perforation	0	1 (0.1)
Gastroesophageal reflux disease	0	1 (0.1)
Upper gastrointestinal hemorrhage	0	1 (0.1)

This reviewer created this table using the 90-Day Safety IDB ADAE dataset, AESER = Y, TEPCDLFL.

13.2. TEAEs by Preferred Term and Groups of Preferred Terms
Belonging to SOC of Gastrointestinal Disorders with Incidence of at
Least 0.3% Higher in Donanemab Arm Compared to Placebo in the
Placebo-Controlled Pool

The following table shows TEAEs by preferred term and groups of preferred terms with incidence of at least 0.3% higher in the donanemab arm compared to placebo in the placebo-controlled pool.

Table 151. TEAEs by Preferred Term and Groups of Preferred Terms Belonging to SOC of Gastrointestinal Disorders with Incidence of at Least 0.3% Higher in the Donanemab Arm Compared to Placebo in the Placebo-controlled Pool

Preferred Terms and Grouped Preferred Terms	Donanemab N=984 n (%)	Placebo N=999 n (%)
TEAEs Belonging to GI SOC	206 (20.9)	192 (19.2)
Nausea	49 (5)	37 (3.7)
TEAEs Belonging to Intestinal Obstruction	5 (0.5)	0
Small intestinal obstruction	4 (0.4)	0
Intestinal obstruction	1 (0.1)	0
Gastroesophageal reflux disease	17 (1.7)	12 (1.2)
Vomiting	31 (3.2)	27 (2.7)
Pancreatic cyst	3 (0.3)	0
Dysphagia	7 (0.7)	4 (0.4)
Dental caries	9 (0.9)	6 (0.6)
TEAEs Related to Hernia	10 (1.0)	7 (0.7)
Inguinal hernia	9 (0.9)	5 (0.5)
Femoral hernia strangulated	1 (0.1)	0
Hiatus hernia	4 (0.4)	5 (0.5)
Abdominal hernia	0	1 (0.1)
Umbilical hernia	0	2 (0.2)

The reviewer created this table using the 90 Day Safety Update ADAE, TEPCLYFL = Y, APERIODC = First treatment, AESOC = GI.

13.3. Select TEAEs and Grouped TEAEs Belonging to the GI SOC with Incidence of Less than 0.3% Higher in the Donanemab Arm Compared to Placebo in the Placebo-controlled Pool

The following table shows the incidence of select TEAEs and groups of TEAEs belonging to the GI SOC with incidence of less than 0.3% higher in the donanemab arm compared to placebo in the placebo-controlled pool.

Table 152. Select TEAEs and Grouped TEAEs Belonging to the GI SOC with Incidence of Less than 0.3% Higher in the Donanemab Arm Compared to Placebo in the Placebo-controlled Pool

Grouped Terms	Donanemab N=984 n (%)	Placebo N=999 n (%)
TEAEs Related to the Topic of Gastritis, Duodenitis, Esophagitis	26 (2.6)	24 (2.4)
Chronic gastritis	1 (0.1)	0
Duodenal ulcer	0	1 (0.1)
Duodenitis	1 (0.1)	1 (0.1)
Dyspepsia	1 (0.1)	3 (0.3)
Gastric antral vascular ectasia	0	1 (0.1)
Gastric ulcer perforation	0	1 (0.1)
Gastritis	3 (0.3)	3 (0.3)
Gastritis erosive	1 (0.1)	0
Gastroesophageal reflux disease	17 (1.7)	12 (1.2)
Esophagitis	4 (0.4)	2 (0.2)
Reflux gastritis	1 (0.1)	1 (0.1)
Upper gastrointestinal hemorrhage	1 (0.1)	1 (0.1)
Grouped Terms of Intestinal Perforation	2 (0.2)	1 (0.1)
Intestinal perforation	1 (0.1)	0
Large intestine perforation	1 (0.1)	0
Small intestinal perforation	0	1 (0.1)
TEAEs Related to Pancreatitis	3 (0.3)	2 (0.2)
Pancreatitis acute	2 (0.2)	0
Pancreatitis	1 (0.1)	1 (0.1)
Obstructive pancreatitis	0	1 (0.1)
Obstruction gastric	1 (0.1)	0
Gastroenteritis	1 (0.1)	0
TEAES Related to Colitis	5 (0.5)	4 (0.4)
Colitis microscopic	2 (0.2)	0
Clostridium difficile colitis	1 (0.1)	0

Grouped Terms	Donanemab N=984 n (%)	Placebo N=999 n (%)
Colitis ischemic	1 (0.1)	0
Enterocolitis viral	1 (0.1)	0
Colitis	1 (0.1)	4 (0.4)
Melena	1 (0.1)	1 (0.1)
Lower gastrointestinal hemorrhage	0	1 (0.1)
TEAEs Related to Esophageal Obstruction or Esophageal Stenosis	1 (0.1)	2 (0.2)
Esophageal Stenosis	1 (0.1)	1 (0.1)
Esophageal Obstruction	0	1 (0.1)
Dyspepsia	1 (0.1)	3 (0.3)
Constipation	18 (1.8)	23 (2.3)

The reviewer created this table using the 90 Day Safety Update ADAE, TEPCLYFL = Y, APERIODC = First treatment, AESOC = GI.

13.4. Incidence of TEAEs Belonging to the Gastrointestinal Disorder SOC in the Placebo-controlled Pool

The following table includes TEAEs belonging to the Gastrointestinal Disorder SOC in the placebo-controlled pool.

Table 153. TEAEs Belonging to the Gastrointestinal Disorder SOC in the Placebo-controlled Pool

Grouped Terms	Donanemab N=984 n (%)	Placebo N=999 n (%)
TEAEs Belonging to GI SOC	206 (20.9)	192 (19.2)
Nausea	49 (5)	37 (3.7)
Gastroesophageal reflux disease	17 (1.7)	12 (1.2)
Vomiting	31 (3.2)	27 (2.7)
Inguinal hernia	9 (0.9)	5 (0.5)
Small intestinal obstruction	4 (0.4)	0
Dental caries	9 (0.9)	6 (0.6)
Pancreatic cyst	3 (0.3)	0
Dysphagia	7 (0.7)	4 (0.4)
Colitis microscopic	2 (0.2)	0
Feces discolored	2 (0.2)	0
Esophagitis	4 (0.4)	2 (0.2)
Pancreatitis acute	2 (0.2)	0

Grouped Terms	Donanemab N=984 n (%)	Placebo N=999 n (%)
Tooth impacted	2 (0.2)	0
Toothache	4 (0.4)	2 (0.2)
Flatulence	3 (0.3)	1 (0.1)
Abdominal discomfort	6 (0.6)	4 (0.4)
Abdominal pain	15 (1.5)	13 (1.3)
Large intestine polyp	4 (0.4)	3 (0.3)
Abdominal tenderness	1 (0.1)	0
Anal cyst	1 (0.1)	0
Anal fistula	1 (0.1)	0
Chapped lips	1 (0.1)	0
Chronic gastritis	1 (0.1)	0
Colitis ischemic	1 (0.1)	0
Crohn's disease	1 (0.1)	0
Diverticulum intestinal	2 (0.2)	1 (0.1)
Enterovesical fistula	1 (0.1)	0
Feces soft	1 (0.1)	0
Femoral hernia strangulated	1 (0.1)	0
Gastritis erosive	1 (0.1)	0
Gastrointestinal disorder	1 (0.1)	0
Gingival pain	1 (0.1)	0
Intestinal obstruction	1 (0.1)	0
Intestinal perforation	1 (0.1)	0
Large intestine perforation	1 (0.1)	0
Lip swelling	1 (0.1)	0
Obstruction gastric	1 (0.1)	0
Odynophagia	1 (0.1)	0
Palatal disorder	1 (0.1)	0
Plicated tongue	1 (0.1)	0
Proctalgia	1 (0.1)	0
Retroperitoneal hemorrhage	1 (0.1)	0
Salivary gland mass	1 (0.1)	0
Stomatitis	1 (0.1)	0
Tongue movement disturbance	1 (0.1)	0
Tooth loss	1 (0.1)	0
Anal incontinence	3 (0.3)	2 (0.2)
Hemorrhoids	3 (0.3)	2 (0.2)

Grouped Terms	Donanemab N=984 n (%)	Placebo N=999 n (%)
Abdominal pain upper	6 (0.6)	6 (0.6)
Acquired esophageal web	1 (0.1)	1 (0.1)
Duodenitis	1 (0.1)	1 (0.1)
Eructation	1 (0.1)	1 (0.1)
Gastric polyps	1 (0.1)	1 (0.1)
Gastritis	3 (0.3)	3 (0.3)
Hematochezia	4 (0.4)	4 (0.4)
Melaena	1 (0.1)	1 (0.1)
Esophageal stenosis	1 (0.1)	1 (0.1)
Pancreatitis	1 (0.1)	1 (0.1)
Reflux gastritis	1 (0.1)	1 (0.1)
Upper gastrointestinal hemorrhage	1 (0.1)	1 (0.1)
Hiatus hernia	4 (0.4)	5 (0.5)
Periodontal disease	2 (0.2)	3 (0.3)
Rectal hemorrhage	2 (0.2)	3 (0.3)
Abdominal distension	0	1 (0.1)
Abdominal hernia	0	1 (0.1)
Abdominal wall disorder	0	1 (0.1)
Abdominal wall hematoma	0	1 (0.1)
Anal stenosis	0	1 (0.1)
Change of bowel habit	0	1 (0.1)
Dry mouth	1 (0.1)	2 (0.2)
Duodenal ulcer	0	1 (0.1)
Gastric antral vascular ectasia	0	1 (0.1)
Gastric ulcer perforation	0	1 (0.1)
Hypoesthesia oral	0	1 (0.1)
Intestinal mass	0	1 (0.1)
Intestinal polyp	0	1 (0.1)
Loose tooth	0	1 (0.1)
Lower gastrointestinal hemorrhage	0	1 (0.1)
Mouth swelling	0	1 (0.1)
Mouth ulceration	0	1 (0.1)
Obstructive pancreatitis	0	1 (0.1)
Esophageal obstruction	0	1 (0.1)
Palatal ulcer	0	1 (0.1)
Pneumoperitoneum	0	1 (0.1)

Grouped Terms	Donanemab N=984 n (%)	Placebo N=999 n (%)
Rectal prolapse	0	1 (0.1)
Salivary duct obstruction	0	1 (0.1)
Salivary gland pain	0	1 (0.1)
Small intestinal perforation	0	1 (0.1)
Dyspepsia	1 (0.1)	3 (0.3)
Ascites	0	2 (0.2)
Fecaloma	0	2 (0.2)
Food poisoning	0	2 (0.2)
Umbilical hernia	0	2 (0.2)
Diarrhea	51 (5.2)	55 (5.5)
Colitis	1 (0.1)	4 (0.4)
Diverticulum	1 (0.1)	4 (0.4)
Abdominal pain lower	1 (0.1)	5 (0.5)
Irritable bowel syndrome	0	4 (0.4)
Constipation	18 (1.8)	23 (2.3)

The reviewer created this table using the 90 Day Safety Update ADAE, TEPCLYFL = Y, APERIODC = First treatment, AESOC = GI.

13.5. Narrative for Subject with TEAE of Microscopic Colitis

TEAE of Microscopic colitis, IST-MC-AACI- (b) (6)

68 year-old female with past medical history of AD, depression, sinus bradycardia, diverticulosis, history of pulmonary embolism, Grave's disease, and thyroid cancer who developed the TEAE of microscopic colitis (verbatim term: microscopic collagenous colitis, moderate severity) on Study Day 342, 7 days after the 13th donanemab dose. The Applicant reported that the diagnosis was made by colonoscopy after the subject had experienced frequent bouts of diarrhea.¹⁵¹ She was treated with sulfasalazine from Study Day 342 to 386 and then started on probiotics NOS on Study Day 386. The dose was not changed, and the subject went on to receive an additional six doses of study drug. The outcome of the TEAE was noted as not recovered/not resolved at the time of the data cutoff. The subject was also noted to have started concomitant ibuprofen PRN use from Study Day 201 to 372 for the development of left arm pain.

¹⁵¹ Noted by the Applicant in a response dated December 5, 2023, to an information request dated December 4, 2023.

Clinical Review
Natalie Branagan, MD
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Reviewer comment: A role for donanemab in the case cannot be ruled out given an absence of risk factors except for concomitant ibuprofen use, which has been associated with colitis.¹⁵²

13.6. References

References are included in footnotes in this review.

13.7. Financial Disclosure

APPEARS THIS WAY ON ORIGINAL

¹⁵² Tonolini M. Acute nonsteroidal anti-inflammatory drug-induced colitis. J Emerg Trauma Shock. 2013 Oct-Dec; 6(4): 301–303.
doi: 10.4103/0974-2700.120389: 10.4103/0974-2700.120389

Clinical Review
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The reader is referred to the review of clinical efficacy by Dr. Kevin Krudys for financial disclosures.

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

/s/

NATALIE M BRANAGAN
06/28/2024 01:39:53 PM

SALLY U YASUDA
06/28/2024 01:45:14 PM

Clinical Review
Kevin Krudys, PhD
BLA 761248
Kisunla (donanemab)

CLINICAL REVIEW

Application Type	BLA
Application Number(s)	761248
Priority or Standard	Priority
Submit Date(s)	09/03/2021, 03/04/2022, 05/18/2022
Received Date(s)	05/18/2022
PDUFA Goal Date	01/18/2023
Division/Office	Division of Neurology 1/Office of Neuroscience
Reviewer Name(s)	Kevin Krudys, PhD
Review Completion Date	01/17/2023
Established/Proper Name	Donanemab
(Proposed) Trade Name	Kisunla
Applicant	Eli Lilly and Company
Dosage Form(s)	Solution for injection
Applicant Proposed Dosing Regimen(s)	700 mg as an intravenous infusion every four weeks for the first three doses, followed by 1400 mg every four weeks, until brain amyloid plaque is cleared
Applicant Proposed Indication(s)/Population(s)	(b) (4)
Recommendation on Regulatory Action	Accelerated Approval
Recommended Indication(s)/Population(s)	Treatment of Alzheimer's disease

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Glossary

A β	amyloid beta
AC	advisory committee
AD	Alzheimer's disease
ADA	anti-drug antibody
ADAS-Cog	Alzheimer's Disease Assessment Scale – Cognitive Subscale
ADCS-ADL	Alzheimer's Disease Cooperative Study – Activities of Daily Living
ADCS-iADL	Alzheimer's Disease Cooperative Study – instrumental Activities of Daily Living subscale
AE	adverse event
ApoE	apolipoprotein E
ARIA	amyloid-related imaging abnormalities
ARIA-E	amyloid-related imaging abnormalities-edema
ARIA-H	amyloid-related imaging abnormalities-hemorrhage
BACE	β -site amyloid precursor protein cleaving enzyme
BLA	biologics license application
BRF	Benefit Risk Framework
CDER	Center for Drug Evaluation and Research
CDR	Clinical Dementia Rating
CDR-SB	Clinical Dementia Rating Sum of Boxes
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DIAD	dominantly inherited Alzheimer's disease
DMC	data monitoring committee
eCTD	electronic common technical document
FDA	Food and Drug Administration
GCP	good clinical practice
GFAP	glial fibrillary acidic protein
iADRS	integrated Alzheimer's Disease Rating Scale
ICH	International Council for Harmonization
IgG1	immunoglobulin G1
IND	Investigational New Drug Application
ISE	integrated summary of effectiveness

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ITT	intent to treat
LS	least square
mITT	modified intent to treat
MMRM	mixed-effects model repeated measures
MMSE	Mini-Mental State Examination
MRI	magnetic resonance imaging
N3pG	N-terminal, third amino acid, pyroglutamate formation
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NfL	neurofilament light chain
NIA-AA	National Institute on Aging at the National Institutes of Health and the Alzheimer's Association
NME	new molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PET	Positron Emission Tomography
PI	prescribing information or package insert
PK	pharmacokinetics
PKPD	pharmacokinetic-pharmacodynamic
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PRO	patient reported outcome
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
TEAE	treatment emergent adverse event
SUVR	standard uptake value ratio
vMRI	volumetric magnetic resonance imaging

1. Executive Summary

1.1. Product Introduction

Donanemab (previously LY3002813) is a humanized immunoglobulin G1 (IgG1) anti-amyloid beta (A β) monoclonal antibody targeting brain amyloid plaque. Extracellular deposits of A β are one of two pathological hallmarks of Alzheimer's disease, along with intracellular aggregates of hyperphosphorylated tau in the form of neurofibrillary tangles. Different A β species are defined by their size and structure and include monomers, oligomers and protofibrils, and insoluble fibrils and plaques. Accumulation of A β in the brain has been proposed to be an important part of the disease process which precedes neurodegeneration and clinical decline. Donanemab reduces brain A β plaque by targeting the N-terminal, third amino acid, pyroglutamate formation (N3pG) epitope that is present in brain amyloid plaques.

The applicant's proposed indication is

(b) (4)

The application is submitted for accelerated approval based on reduction of amyloid beta plaques. The proposed dosing regimen is an intravenous infusion of 700 mg donanemab over approximately 30 minutes, once every four weeks for the first three doses, followed by 1400 mg every four weeks until amyloid plaque is cleared. Donanemab is available as a 350 mg/20 mL solution in a single-dose vial for intravenous infusion.

Donanemab is a new molecular entity (NME) and is not marketed in any country. The proposed proprietary name is Kisunla.

1.2. Conclusions on the Substantial Evidence of Effectiveness

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The applicant has provided substantial evidence of effectiveness to support accelerated approval. The applicant provided biomarker, efficacy, and safety data from a single adequate and well controlled study that demonstrated that donanemab, as compared to placebo, robustly reduced brain amyloid plaque with statistical significance in patients at the early stages of symptomatic Alzheimer's disease. The Division has previously determined in the reviews of aducanumab and lecanemab that a reduction in amyloid plaque burden measured by PET imaging is reasonably likely to predict clinical benefit. The observed effects of donanemab on clinical endpoints in the study contributed to the reasonable likelihood that a lowering of amyloid beta plaque will result in a clinical benefit.

1.3. **Benefit-Risk Assessment**

Benefit-Risk Integrated Assessment

Donanemab is an anti-amyloid beta (A β) monoclonal antibody targeting aggregated forms of A β , specifically the N3pG epitope that is present solely in brain amyloid plaques, and developed to treat patients with Alzheimer's disease. This reviewer recommends accelerated approval based on biomarker and efficacy information currently available.

Alzheimer's disease is an irreversible and progressive disease that affects memory, thinking, and behavior and is ultimately fatal. After a diagnosis of Alzheimer's dementia, the average survival is 4 to 8 years. Alzheimer's disease is the sixth leading cause of death in the United States. Acetylcholinesterase inhibitors and the N-methyl-D-aspartate receptor antagonist memantine are approved therapies, but they do not target the underlying pathology of the disease and their effects are modest and short-lived. Aducanumab and lecanemab are amyloid beta-directed antibodies that were approved under the accelerated approval pathway based on reduction of brain amyloid plaque as measured by ¹⁸F-florbetapir positron emission tomography (PET) for the treatment of Alzheimer's disease, specifically patients with mild cognitive impairment or mild dementia stage of disease, but their use to date is limited. There remains an urgent and unmet medical need for additional effective treatments for Alzheimer's disease, and a particular unmet need for effective therapies to delay, halt, or reverse the pathophysiological processes that ultimately lead to the clinical deficits of Alzheimer's disease.

This submission contains biomarker, efficacy, and safety data from Study AACG, a multicenter, randomized, double-blind, placebo-controlled, parallel group study in patients with early symptomatic Alzheimer's disease. The study included a 9-week screening period, a 76-week placebo-controlled treatment period, and a 48-week immunogenicity and safety follow-up period. For the placebo-controlled period, patients were

initially randomized to donanemab monotherapy, donanemab in combination with LY3202626 (BACE1 inhibitor), or placebo in a 1:1:1 ratio. Early in the study, the combination therapy arm was discontinued with only 15 patients randomized to this group. The primary objective of the study was to evaluate whether donanemab decreases cognitive and/or functional decline as assessed by the integrated Alzheimer's Disease Rating Scale (iADRS), a simple linear combination of the Alzheimer's Disease Assessment Scale – 13-item Cognitive subscale (ADAS-Cog 13) and the Alzheimer's Disease Cooperative Study – instrumental Activities of Daily Living subscale (ADCS-iADL) at 76 weeks. Change from brain amyloid plaque as measured by ¹⁸F-florbetapir PET was listed as a secondary endpoint in the protocol.

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

The primary safety event identified in the clinical trial is amyloid-related imaging abnormalities (ARIA) which represent a spectrum of imaging findings on brain MRI, including brain edema and brain microhemorrhage. Most patients who experience ARIA do not have symptoms, and when symptoms occur, they are usually mild or moderate. ARIA is a known consequence of anti-amyloid treatment and is mitigated by dose suspensions and discontinuations and MRI monitoring.

The accelerated approval pathway is appropriate for donanemab because Alzheimer's disease is clearly a serious and life-threatening disease, and donanemab has the potential to address an unmet medical need and provide an advantage over available therapy. Amyloid plaque is an underlying, fundamental, and defining pathophysiological feature of Alzheimer's disease. Although the role of amyloid and its relationship to other pathophysiological features of Alzheimer's disease, such as tau and neurodegeneration, is complicated, the presence of amyloid plaques is a primary and essential finding in Alzheimer's disease, including early in the disease. It is reasonable to conclude that treatment that is targeted at reducing amyloid plaque, and that successfully accomplishes that reduction, has the potential to convey clinical benefit. Donanemab treatment results in a robust and statistically significant reduction in brain amyloid plaque with a magnitude that the Division has concluded to be reasonably likely to predict clinical benefit. The effects on amyloid are persuasive and consistent across subgroups, supporting the ability of Study AACG to be considered a single adequate and well-controlled trial that is capable of providing substantial evidence of effectiveness.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	- Alzheimer's disease is a progressive, degenerative brain disorder that affects memory, thinking, and behavior and is the most common cause of dementia. - Clinical symptoms include difficulty remembering recent conversations, names, or events, impaired communication, disorientation, confusion, poor judgment, behavioral changes, and ultimately, difficulty walking, speaking, and swallowing. - Alzheimer's disease exists on a continuum from biological changes in the brain, to subtle problems with memory and thinking, and ultimately difficulties that affect an individual's ability to perform everyday activities. The disease process may begin 20 years or more before symptoms arise. - After a diagnosis of Alzheimer's dementia, the average survival is 4 to 8 years. - An estimated 6.2 million Americans age 65 years and older are currently living with Alzheimer's disease. - Alzheimer's disease is the sixth leading cause of death in the United States. - Almost two-thirds of Americans with Alzheimer's disease are women. Older African Americans and Latinos are disproportionately more likely to have Alzheimer's disease than White Americans.	Alzheimer's disease is a major public health issue which imposes an immense burden on patients and caregivers. The number of Americans with Alzheimer's disease dementia is expected to increase significantly in the next few decades.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Current Treatment Options	• FDA-approved therapies include the acetylcholinesterase inhibitors donepezil, rivastigmine, and galantamine, and the N-methyl-D-aspartate receptor antagonist memantine. Treatment effects of these therapies are modest and transitory. • Antipsychotics are commonly prescribed to treat behavioral symptoms but are not approved for the treatment of Alzheimer’s disease and are associated with increased mortality in older patients. Aducanumab and lecanemab are amyloid beta-directed antibodies approved under the accelerated approval pathway and indicated for the treatment of Alzheimer’s disease, specifically patients with mild cognitive impairment or mild dementia stage of disease.	There is an urgent and unmet medical need for effective treatments for Alzheimer’s disease. In addition to the general need for more effective treatments, there is a particular unmet need for effective treatments to delay, halt, or reverse the pathophysiological processes that ultimately lead to the clinical deficits of Alzheimer’s disease. Aducanumab and lecanemab are effective treatment options in patients at earlier stages of the disease, but their use remains limited.
Benefit	• The efficacy of donanemab in patients at the early stages of symptomatic Alzheimer’s disease was evaluated in Study AACG: ○ Patients were randomized to receive placebo or donanemab ○ The trial enrolled 257 patients: 131 in the donanemab arm and 126 in the placebo arm ○ The primary endpoint was the change from baseline in iADRS. The iADRS is a simple linear combination of the ADAS-Cog 13 and ADCS-iADL. CDR-SB, ADAS-Cog 13, ADCS-iADL, and MMSE were secondary endpoints. ○ Change from brain amyloid plaque as measured by ¹⁸F-florbetapir PET and quantified by a composite SUVR was listed as a secondary endpoint in the protocol. • Donanemab reduced brain amyloid plaque. Brain amyloid plaque showed a reduction from 107.2 Centiloids at baseline to 23.1 Centiloids at Week 76 in the donanemab treatment arm, compared	The applicant has demonstrated a robust and statistically significant treatment-related reduction in brain amyloid plaque in patients at the early stages of symptomatic Alzheimer’s disease. The decrease in brain amyloid plaque demonstrated for donanemab is consistent with the reduction established for aducanumab and lecanemab, drugs that received accelerated approval based on a conclusion that the decrease in brain amyloid plaque was reasonably likely to predict clinical benefit. The observed effects of donanemab on clinical endpoints in the study contributed to the reasonable likelihood that a lowering of amyloid beta plaque will result in clinical

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	to a value of 103.1 at baseline and 104.0 at Week 76 in the placebo arm. The donanemab treatment arm had a statistically significant reduction in brain amyloid plaque from baseline to Week 76 compared to the placebo arm (mean difference of -85.1 Centiloids; $p < 0.001$). • The primary efficacy endpoint analysis, change from baseline in iADRS at Week 76, demonstrated a statistically significant treatment effect in the donanemab treatment arm compared to placebo (3.20 [-32%], $p = 0.042$). • The donanemab treatment regimen demonstrated favorable numerical results on secondary clinical endpoints with nominal statistical significance for ADAS-Cog 13 at Week 76.	benefit.
Risk and Risk Management	• Refer to safety review by Dr. Branagan.	

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application

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

2. Therapeutic Context

2.1. Analysis of Condition

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

and behavior and is the most common cause of dementia. According to a recent report (Alzheimer's Association 2021), an estimated 6.2 million Americans age 65 years and older are currently living with Alzheimer's disease dementia. In the absence of interventions to prevent or slow the disease the number is projected to reach 12.7 million by 2050. The report noted that Alzheimer's disease is the sixth-leading cause of death in the United States and the fifth-leading cause of death for those age 65 and older. Almost two-thirds of Americans with Alzheimer's disease are women. Older African Americans and Latinos are disproportionately more likely to have Alzheimer's disease than White Americans (Alzheimer's Association 2021).

Alzheimer's disease exists on a continuum from pathological changes in the brain which are undetectable to the person affected, to subtle problems with memory and thinking, and ultimately difficulties with memory, language, problem-solving, and other skills that affect an individual's ability to perform everyday activities. The disease process may begin 20 years or more before symptoms arise (Vermunt et al. 2019). Life expectancy varies depending on many factors, but after a diagnosis of Alzheimer's dementia the average survival is 4 to 8 years (Alzheimer's Association 2021). The long duration of the disease contributes to the burden not only on the individuals with the disease, but also their families and caregivers who provide most of the patient care and are at an increased risk for emotional distress and negative mental and physical outcomes.

The two pathological hallmarks of Alzheimer's disease are extracellular deposits of A β , or plaques, and intracellular aggregates of hyperphosphorylated tau in the form of neurofibrillary tangles. Accumulation of A β in the brain has been proposed to be the primary driver of the disease process and precedes the accumulation of tau pathology and neural degeneration. Consequently, therapies to inhibit A β production or enhance A β clearance have been investigated in an attempt to slow or halt the disease process. Importantly, "anti-amyloid" therapies are not a distinct class of drugs, but rather reflect many different modes of action. A careful examination of anti-A β therapies has revealed that for therapies targeting aggregated forms of A β there exists a relationship between reduction of brain amyloid plaque and reduction of clinical decline.

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

2.2. Analysis of Current Treatment Options

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

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

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

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Donanemab is a new molecular entity (NME) and is not currently marketed in the United States for any indication.

3.2. Summary of Presubmission/Submission Regulatory Activity

IND 109157 for donanemab (previously LY3002813) was opened in the United States on February 5, 2013, for (b) (4) Alzheimer's disease following a pre-IND meeting between the applicant and FDA on October 14, 2010. Relevant regulatory interactions between FDA and the applicant include the following:

- August 1, 2014 – Written responses were provided in response to a Type C meeting request. The primary focus of this meeting was to provide feedback (b) (4)
- December 7, 2015 – Written responses were provided in response to a Type C meeting request for feedback on the design and safety monitoring plan for a Phase 1b study (AACD).
- July 20, 2018 – Fast Track designation was granted.
- March 2, 2021 – The results of Study AACG were discussed at a Type C meeting. The Division stated that the result of Study AACG did not appear capable of providing substantial evidence of effectiveness as a single study. The Division also disagreed with the sponsor's proposal to prospectively specify the use of the integrated Alzheimer's Disease Rating Scale (iADRS) as the primary efficacy measure for Study AACI.

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- June 21, 2021 – Donanemab was granted Breakthrough Therapy designation for the treatment of Alzheimer’s disease.
- August 26, 2021 – A Type B meeting was held to discuss the contents of a BLA for accelerated approval. The Division agreed that a rolling submission was acceptable and shared expectations for the safety database at the time of submission.
- September 3, 2021 – The applicant opened BLA 761248 and submitted clinical and nonclinical information.
- May 18, 2022 – BLA submission complete.

3.3. Foreign Regulatory Actions and Marketing History

Donanemab is not approved or marketed in any foreign country.

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

4.1. Office of Scientific Investigations (OSI)

OSI conducted inspections of three clinical sites and an inspection of the sponsor, Eli Lilly and Company. Site selection was based on risk ranking in the clinical investigator site selection tool, number of subjects enrolled, and prior inspection history. The review concludes that Study AACG appears to have been conducted adequately and the data generated by the sites inspected appear acceptable in support of the respective indication.

The review noted that one site was terminated due to good clinical practice (GCP) issues. Although the applicant notified FDA of this site closure, it was not mentioned in the clinical study report. This site only enrolled 3 patients into Study AACG, all of whom discontinued from the study. A sensitivity analysis excluding this site was performed and did not meaningfully change the overall results. The review also noted one instance of unintentional blinding which resulted in the patient being discontinued from the study. Such instances of unintentional blinding are unlikely to affect the conclusions on amyloid plaque reduction.

4.2. Product Quality

Please see the OPQ review for any issues related to product quality.

4.3. Clinical Microbiology

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Not applicable.

4.4. Nonclinical Pharmacology/Toxicology

Please see Dr. Hawver's review for any issues related to nonclinical pharmacology/toxicology.

4.5. Clinical Pharmacology

The clinical pharmacology review team has concluded that the effectiveness of donanemab is supported by amyloid PET reduction in the Phase 1 Study AACD, treatment-response relationships, tau PET data, and plasma biomarker (p-tau217 and GFAP) data. They have also concluded that there is no clinical pharmacology evidence to support dose cessation after achieving a reduction in amyloid PET below a certain value or specific treatment duration.

No dosage adjustments are recommended based on intrinsic and extrinsic factors. There was no significant effect of age, race, sex, renal or hepatic impairment on donanemab exposures. Body weight and ADA titer were identified as covariates to impact donanemab exposures. However, the change in the exposures was not found to have an effect on amyloid PET reduction and therefore, no dose adjustments are warranted.

The review notes minor differences between the pivotal clinical trial (lyophilized) and to-be-marketed (solution) donanemab formulations. The applicant performed supportive studies to compare the formulations and OBP confirmed that the applicant has provided adequate comparability studies to demonstrate that the to-be-marketed product and the pivotal clinical trial formulation are comparable.

The review team recommends accelerated approval.

Please see Dr. Nookala's review for further details.

4.6. Devices and Companion Diagnostic Issues

Not applicable.

4.7. Consumer Study Reviews

Not applicable.

5. Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

The primary study pertinent to the evaluation of efficacy is presented in Table 1.

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Table 1: Tabular Presentation of the Clinical Study Contributing Efficacy Data Relevant to the Review of this BLA

Trial Identity/NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population (per categorization at the time of enrollment)	No. of Centers and Countries
<i>Controlled Studies to Support Efficacy and Safety</i>							
IST-MC-AACG (Study AACG)/NCT03367403	Double-blind, placebo-controlled, parallel group	IV infusion over at least 30 minutes <u>Placebo</u> Saline infusion <u>Donanemab</u> 700 mg every four weeks for first 3 doses, followed by 1400 mg every 4 weeks until brain amyloid reaches predefined levels or for a total of 72 weeks *the original design included a combination therapy arm of donanemab and LY3202626 (BACE1 inhibitor)	<u>Primary</u> Change from baseline in iADRS at 18 months <u>Secondary</u> Change from baseline in CDR-SB, ADAS-Cog 13, ADCS-iADL, MMSE, brain amyloid plaque, brain tau, and vMRI measures at 18 months	72-week treatment period 48-week follow-up period	272	Consistent with a diagnosis of MCI due to Alzheimer’s disease or mild Alzheimer’s disease dementia based on operationalized criteria from the 2018 NIA-AA Research Framework for Alzheimer’s disease MMSE score of 20 to 28 Positive amyloid load and specific tau criteria by PET 60 to 85 years of age	56 centers in United States and Canada

5.2. Review Strategy

The applicant presents Study AACG as the primary study supporting the submission with supportive data from single- and multiple-ascending dose studies AACC and AACD. Studies AACC and AACD are not required to establish an effect of donanemab on brain amyloid and do not inform the reasonable likelihood of brain amyloid plaque as a surrogate endpoint and are therefore not reviewed.

Although listed as a secondary endpoint in the Study AACG protocol, change from baseline in brain amyloid plaque as measured by ^{18}F -florbetapir PET is proposed as the surrogate endpoint that is reasonably likely to predict clinical benefit, and is therefore the focus of this review. The clinical efficacy endpoint results are reviewed in the context of whether they support the likelihood of the surrogate to predict clinical benefit, rather than whether they directly provide substantial evidence of effectiveness of clinical benefit for full approval.

The acceptability of a reduction in brain amyloid plaque to serve as a surrogate endpoint that is reasonably likely to predict clinical benefit has been addressed in the review of aducanumab and is therefore not reconsidered here. It is important to note, however, that the publicly-reported topline results from both the lecanemab and gantenerumab programs appear to be entirely consistent with the relationship between plaque reduction and change in clinical endpoints that was established in the aducanumab review.

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

6. Review of Relevant Individual Trials Used to Support Efficacy

6.1. Study AACG (I5T-MC-AACG) Assessment of Safety, Tolerability, and Efficacy of LY3002813 in Early Symptomatic Alzheimer's Disease

6.1.1. Study Design

Overview and Objective

Study AACG was a double-blind, placebo-controlled study in patients with early symptomatic Alzheimer's disease. The primary objective of the study was to evaluate whether donanemab decreases cognitive and/or functional decline as assessed by the integrated Alzheimer's Disease Rating Scale (iADRS) at 76 weeks.

Trial Design

Study AACG was a multicenter, randomized, double-blind, placebo-controlled, parallel group study in patients with early symptomatic Alzheimer's disease. A total of 56 centers in the United States and Canada enrolled patients into the trial. Randomization was stratified by investigative site only. The study included a 9-week screening period, a 76-week placebo-controlled treatment period, and a 48-week immunogenicity and safety follow-up period. For the placebo-controlled period, patients were initially randomized to donanemab monotherapy, donanemab in combination with LY3202626 (BACE1 inhibitor), or placebo in a 1:1:1 ratio. Early in the study, the combination therapy arm was discontinued with only 15 patients randomized to this group. The study did not include a long-term extension.

Diagnostic Criteria

The protocol did not specify a formal clinical diagnosis of Alzheimer's disease, but the inclusion criteria are consistent with a diagnosis of MCI due to Alzheimer's disease or mild Alzheimer's disease dementia based on operationalized criteria from the 2018 NIA-AA Research Framework for Alzheimer's disease (Jack et al. 2018). Patients were required to have evidence of A β pathology by quantitative assessment on PET and evidence of a topographic tau disposition pattern consistent with Alzheimer's disease. Patients were also required to have progressive change in memory function for at least 6 months and evidence of a mild degree of cognitive impairment on a screening cognitive assessment.

Key Inclusion Criteria

1. Gradual and progressive change in memory function reported by patients or informants for ≥ 6 months
2. MMSE score of 20 to ≤ 28
3. Male or female patients age 60 to ≤ 85 years
4. Must have a study partner who is in frequent contact with the patient (at least 10 hours per week)
5. Confirmed presence of amyloid plaques on PET (SUVR ≥ 1.17 or ≥ 37 Centiloids)
6. Confirmed presence of intermediate tau on PET (tau SUVR between 1.10 and 1.46)
Patients with SUVR < 1.10 were excluded except for patients with a topographical deposition pattern consistent with extensive tau spread

Reviewer Comment: Earlier versions of the protocol did not include a criterion for MMSE. Instead, patients were to have a CogState Brief Battery learning/working memory score of 82 to 90. This appears to contribute to the fraction of patients (7%) randomized in the study who have MMSE scores < 20 , with a minimum score of 13. The CogState Brief Battery criterion was removed and replaced by the MMSE criterion in later versions of the protocol.

Notably, the applicant did not require a formal clinical diagnosis of mild cognitive impairment due to Alzheimer's disease or mild Alzheimer's disease dementia. Instead, patients were enrolled based on Alzheimer's disease pathology and presence of clinical symptoms and objective evidence of cognitive impairment with scoring in the mild range as assessed by either CogState Brief Battery or MMSE. These criteria essentially operationalized the 2018 NIA-AA Research Framework for Alzheimer's disease (Jack et al. 2018) (A+/T+/evidence of cognitive impairment and decline in cognitive performance from baseline). Enrollment criteria for functional status were not specified, but the population would either have no functional impairment or some degree of functional impairment with only a mild range of impairment in cognition which would also be consistent with clinical staging for mild cognitive impairment or mild dementia, although it is noted that there is potential for some patients with a greater degree of functional impairment suggesting a moderate stage of dementia to be enrolled using these criteria.

The specific quantitative criteria for amyloid and tau PET were selected to enrich the population such that patients would be more likely to experience clinical progression during the study and more likely to respond to an anti-amyloid therapy. The applicant hypothesized that patients with higher tau levels would have more advanced disease and more limited efficacy and therefore excluded them. These maneuvers were designed to improve the signal to noise ratio in a small study and do not need to be replicated in labeling, other than requiring the presence of amyloid beta pathology. This can be accomplished with visual read as there is a high degree of concordance between visual reads and quantitative assessment. The confirmatory study will further inform the potential for baseline tau levels to influence the effectiveness of donanemab.

Key Exclusion Criteria

1. Significant neurological disease affecting the central nervous system, other than Alzheimer's disease, that may affect cognition or ability to complete the study
2. Current serious or unstable illnesses including cardiovascular, hepatic, renal, gastroenterologic, respiratory, endocrinologic, psychiatric, immunologic, or hematologic diseases that could interfere with study procedures
3. History of clinically significant multiple or severe drug allergies, or severe post-treatment hypersensitivity reactions
4. Modified Hachinski Ischemia Scale score of ≥ 4
5. Screening MRI showing evidence of a significant abnormality that would suggest another potential etiology for progressive dementia
6. MRI demonstrating presence of ARIA-E, >4 cerebral microhemorrhages, more than 1 area of superficial siderosis, any macrohemorrhage or severe white matter disease
7. Treatment with a stable dose of an acetylcholinesterase inhibitor and/or memantine for less than 2 months before randomization
8. Prior treatment with passive anti-amyloid immunotherapy <5 half-lives or active immunization against A β in any other study

Dose Selection

The dosing regimen was based on safety, PK, and PD results from earlier dose-ranging studies and was chosen to balance amyloid plaque reduction and occurrence of ARIA. Briefly, doses lower than 10 mg/kg (equivalent to 700 mg in a 70 kg individual) were not associated with robust amyloid plaque reduction and a single dose of 40 mg/kg (equivalent to 2800 mg in a 70 kg individual) was associated with an unacceptable risk of ARIA. Therefore, a dose of 1400 mg was chosen as the target dose, with a titration schedule of 700 mg for the first 3 doses to reduce the risk of ARIA. The protocol mandated dose reduction and dose cessation based on meeting specific brain amyloid thresholds. The applicant argues that amyloid plaque is the only amyloid species engaged by donanemab and therefore there is no reason to continue dosing once amyloid plaque has been reduced below a certain level.

Reviewer Comment: The decision to cease dosing once amyloid plaque is reduced below a certain threshold is not unreasonable, but there is remaining uncertainty regarding the applicant's approach as there is no evidence that such changes in dosing lead to improvements in clinical outcomes. The threshold commonly used to denote amyloid negativity is a useful measure, but it is still possible there could be added benefit to reducing amyloid further in this patient population. Also, in Study AACG no patients were dosed for more than 72 weeks, specifically those patients who did not reach the amyloid threshold during the study.

Study Treatments

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

Assignment to Treatment

An interactive web response system (IWRS) was used to assign patients to treatment groups. Patients were randomized equally to placebo or donanemab. Randomization was stratified by investigative site only.

Blinding

Study drug was dispensed by an unblinded pharmacist at each site. All other study site staff and patients were blinded to treatment assignment. The site clinical study team remained blinded to any potential changes in amyloid or tau as measured by follow-up PET scans. The protocol did not specify that raters responsible for collection of efficacy assessments were to be blinded

from safety assessments, although raters were instructed to avoid looking at MRI results and disclosure of ARIA events to raters was discouraged.

Dose Modifications/Dose Discontinuation

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

Dose modification criteria were established to account for the expected occurrence of ARIA-E and ARIA-H. Dose reduction or suspension were dependent on the radiographic severity of ARIA-E as detected by MRI, the presence or absence of clinical symptoms, and the severity of symptoms, if present (Table 2). If a dose reduction was required, donanemab was reduced from 1400 mg to 700 mg or from 700 mg to placebo. For cases which did not call for a protocol-mandated temporary discontinuation, the investigator could have chosen to temporarily discontinue donanemab after discussion with the applicant. If a patient had a second occurrence of ARIA-E and had previously been dose reduced or temporarily discontinued from donanemab, then donanemab was permanently discontinued. Donanemab was permanently discontinued in patients with any increase in ARIA-H accompanied by clinically significant symptoms or >4 new microhemorrhages, >1 new area of superficial siderosis, or any macrohemorrhage regardless of symptoms.

Table 2: Dose Modification/Suspension Rules for First Occurrence of ARIA-E

Clinical Symptom Severity	ARIA-E Severity on MRI		
	Mild	Moderate	Severe
No symptoms	Continue dosing	Dose reduction	Temporary discontinuation
Mild	Dose reduction	Temporary discontinuation	Temporary discontinuation
Moderate	Temporary discontinuation	Temporary discontinuation	Temporary discontinuation
Severe	Temporary discontinuation	Temporary discontinuation	Temporary discontinuation

Created by the reviewer, modified from Table AACG.7.2 in the protocol

Administrative Structure

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An independent Data Monitoring Committee (DMC) was formed to monitor the study and review safety on an ongoing basis. PET scans were analyzed by a centralized imaging vendor.

Procedures and Schedule

The schedule for key assessments is provided in Table 3. The pre-randomization period consisted of screening visits within a 63-day period before administration of the first dose. Eligible subjects reported to the study site every 4 weeks for 76 weeks with follow-up visits beginning 12 weeks after the last dose.

Table 3: Study AACG Schedule of Key Assessments

Assessment	Schedule
Eligibility Criteria	Screening, Weeks 0, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, 56, 60, 64, 68, 72
ApoE Genotyping	Week 0
Neurological and Physical Examinations	Screening, Weeks 0, 12, 24, 36, 52, 64, 76, Early Discontinuation
MRI	Screening, Weeks 4, 12, 16, 24, 36, 52, 76, Early Discontinuation
Study Drug Administration	Weeks 0, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, 56, 60, 64, 68, 72
Anti-Donanemab Ab	Weeks 0, 4, 8, 12, 16, 24, 36, 52, 76, Early Discontinuation, Follow-up
Donanemab Concentration	Weeks 0, 4, 8, 12, 16, 24, 36, 52, 64, 72, 76, Early Discontinuation, Follow-up
Blood for Biomarker Analysis	Weeks 0, 12, 24, 36, 52, 64, 76, Early Discontinuation
Amyloid PET	Screening, Weeks 24, 52, 76, Early Discontinuation
Tau PET	Screening, Week 76, Early Discontinuation
MMSE	Screening, Weeks 12, 24, 36, 52, 64, 76, Early Discontinuation
CDR-SB, ADAS-Cog13, ADCS-ADL	Weeks 0, 12, 24, 36, 52, 64, 76, Early Discontinuation

Created by the reviewer, modified from Schedule of Activities table in protocol

Concurrent Medications

Treatment of Alzheimer's disease with cholinesterase inhibitors and/or memantine and/or Axona was allowed if patients had been given the drug for at least 4 months and stable dosing had been maintained for at least 2 months before randomization. If a patient started, changed dose, or stopped any of these medications, the investigator was to contact the applicant to determine whether the patient should continue in the study.

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

- Immunoglobulin therapy was not allowed during the study.

- Concomitant medications that affect CNS function could be given during the study if the dose remained unchanged from 1 month before screening.
- Drugs known to prolong the QT interval were excluded.

Subject Completion, Discontinuation, or Withdrawal

Completers were defined as patients who were randomized to donanemab or placebo with a baseline and at least one post-baseline iADRS result and had disposition status of complete or had 2 weeks exposure in visit interval 21 (Week 76).

Patients permanently discontinuing from study treatment could have remained in the trial. Patients who prematurely discontinued from the study were to return for early discontinuation and follow-up visits with clinical assessments as outlined in Table 3. Drug-specific reasons for protocol-specified discontinuation include ARIA, infusion reactions, and hepatic event or liver test abnormality. Reasons for study discontinuation captured by the case report form (CRF) include AEs, withdrawal by participant, death, caregiver circumstance, physician decision, protocol deviation, or other.

Study Endpoints

Surrogate Endpoint

Amyloid PET standardized uptake value ratio (SUVR) is a quantitative measure of cerebral amyloid plaque burden. Change from baseline in brain amyloid plaque as measured by ¹⁸F-florbetapir PET and quantified by a composite SUVR was assessed at Week 24, Week 52, and Week 76 and listed as a secondary endpoint in the protocol. The primary amyloid PET analysis was the SUVR calculated for a composite summary region of 6 cortical regions (anterior cingulate, posterior cingulate, medial orbital frontal, lateral temporal, lateral parietal, and precuneus) with whole cerebellum as a reference region. 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. Centiloid is a 100-point scale independent of tracer or method which is an average value of 0 in high certainty amyloid negative individuals and 100 in typical Alzheimer's disease patients.

A centralized imaging laboratory was selected to analyze PET scans. Readers were blinded to study treatment but not to the time of assessment.

The Division has previously determined in the review of aducanumab that a reduction in amyloid plaque burden measured by PET imaging is reasonably likely to predict clinical benefit. Amyloid plaque is an underlying, fundamental, and defining pathophysiological feature of

Alzheimer's disease. Although the role of amyloid and its relationship to other pathophysiological features of Alzheimer's disease, such as tau and neurodegeneration, is complicated, the presence of amyloid plaques is a primary and essential finding in Alzheimer's disease, including early in the disease. It is reasonable to conclude that treatment that is targeted at reducing amyloid plaque, and that successfully accomplished that reduction, has the potential to convey clinical benefit.

Primary Endpoint

The primary endpoint was the change from baseline in integrated Alzheimer's Disease Rating Scale (iADRS) at Week 76. The iADRS is a simple 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).

Reviewer's Comment: iADRS was chosen as the primary endpoint in Study AACG without feedback or input from the Division. In the meeting minutes of the March 2, 2021, Type C Meeting discussing the confirmatory study (AACI), 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."

Secondary Endpoints

CDR-SB

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

ADAS-Cog 13

The ADAS-Cog is a cognitive assessment consisting of clinical ratings and cognitive tasks that was originally developed for use in clinical trials of patients with later stages of Alzheimer's

disease dementia. ADAS-Cog 11 includes 11 tasks measuring disturbances of memory, language, and praxis. Many of the items of the ADAS-Cog 11 are at the measurement floor in patients with mild disease and may not show decline over the length of a typical clinical trial. Therefore, two additional tasks, delayed word recall and number cancellation, were added to create the ADAS-Cog 13 for use in this earlier disease population. The ADAS-Cog 13 includes 9 items that test performance (up to 65 points) and 4 clinician-rated items that test language and memory (up to 20 points) for a total score ranging from 0 to 85, with higher scores indicating greater cognitive impairment. The 13 items assess word recall, ability to follow commands, constructional praxis, naming, ideation praxis, orientation, word recognition, comprehension of spoken language, memory, word-finding, language ability, delayed word recall, and concentration.

iADL

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

MMSE

The MMSE is a widely used performance-based assessment of cognitive ability consisting of 11 tasks evaluating orientation, word recall, attention and calculation, language, and visuospatial functions. The scores from the 11 tests are summed to obtain a total score, which ranges from 0 to 30, with lower scores indicating greater cognitive impairment. It is often used as a screening assessment in clinical practice or as a staging instrument for trial inclusion and is also used as an efficacy assessment in clinical trials.

Pharmacodynamic Endpoints

Key biomarker and pharmacodynamic endpoints included the following:

- Change from baseline in brain tau deposition through 76 weeks as measured by PET
- Change from baseline in brain volumes through 76 weeks as measured by vMRI
- Change from baseline in plasma levels of p-tau 217, glial fibrillary acidic protein (GFAP), and neurofilament light chain (NfL)

Statistical Analysis Plan

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The original Statistical Analysis Plan (SAP) was approved in April 2020, and was amended in December 2020, prior to unblinding of the study data.

Definition of Statistical Analysis Populations

The following analysis populations were the key populations defined in the SAP:

- Randomized – all entered patients who are randomized to study treatment
- Full Analysis Set – all randomized patients to donanemab or placebo with a baseline and at least one post-baseline iADRS result

Analysis Method for Amyloid PET

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

Analysis Methods for Clinical Endpoints

The analyses of clinical endpoints used the Full Analysis Set. Change from baseline for clinical endpoints was assessed with MMRM including the terms baseline score, pooled investigator, treatment, visit, treatment-by-visit interaction, baseline-by-visit interaction, concomitant Alzheimer's disease medication use at baseline, and age at baseline. A Bayesian posterior probability of donanemab being superior to placebo by at least 25% was also calculated.

Adjustments for Multiplicity

Bretz's graphical approach was used to control the study-wise type I error rate for the primary and key secondary endpoints at an alpha level of 0.05. If the primary statistical analysis was statistically significant, analyses were to be performed on CDR-SB, ADAS-Cog 13, iADL, and MMSE to determine statistical significance for secondary endpoints.

Subgroup Analyses

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

- ApoE ϵ 4 carrier status (carrier or non-carrier)
- Baseline MMSE ($20 \leq \text{MMSE} \leq 26$ and $\text{MMSE} \geq 27$)
- Tau PET level at baseline: no tau ($\text{SUVR} < 1.10$), low tau ($1.10 \leq \text{SUVR} < 1.23$), and

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medium tau (SUVR ≥ 1.23)

Protocol Amendments

The original protocol was issued on August 30, 2017, and was amended 4 times. MMSE was added as a screening test in version (c) of the protocol. The removal of LY3202626 as a combination therapy was implemented in the current version of the protocol (d).

6.1.2. Study Results

Compliance with Good Clinical Practices

The applicant attests that the study was conducted with the principles of GCP and applicable laws and regulations.

Financial Disclosure

The applicant has adequately disclosed financial interests or agreements with clinical investigators as outlined in the guidance for industry Financial Disclosures by Clinical Investigators.

Patient Disposition

A total of 1955 patients were screened for entry into the study and 272 patients continued to randomization. The most common reason for screen failure (30%) was failure to meet the baseline tau criterion. There were 15 patients who were randomized to the combination therapy arm (donanemab and BACE inhibitor) prior to its termination. One patient randomized to placebo did not receive study treatment. Patient disposition is summarized in Table 4. The greater percentage of discontinuations in the donanemab arm was driven by occurrence of adverse events, specifically infusion-related reactions and ARIA.

Table 4: Study AACG Patient Disposition

Disposition	Study AACG	
No. of patients screened	1955	
No. of patients not randomized	1683	
	Donanemab N=131 n (%)	Placebo N=126 n (%)
Patients randomized	131	126
Full Analysis Set	125 (95%)	120 (95%)
Discontinued treatment*	49 (37%)	34 (27%)
Adverse event	40 (31%)	9 (7%)
Consent withdrawn by participant	2 (2%)	1 (<1%)

Death	0	1 (<1%)
Caregiver circumstance	0	1 (<1%)
Physician decision	0	1 (<1%)
Protocol deviation	0	1 (<1%)
Other reasons	7 (5%)	20 (16%)
Discontinued study*	37 (28%)	32 (26%)
Adverse event	20 (15%)	6 (5%)
Consent withdrawn by participant	12 (9%)	12 (10%)
Death	1 (<1%)	2 (2%)
Caregiver circumstance	0	2 (2%)
Physician decision	0	1 (<1%)
Protocol deviation	1 (<1%)	1 (<1%)
Other reasons	3 (2%)	8 (6%)

Created by reviewer using Figure AACG.4.1 in Study AACG CSR

*Percentages are based on number of patients treated (i.e., excluding one patient randomized to placebo who did not receive treatment)

Protocol Violations/Deviations

There were 75 patients (57%) in the donanemab treatment arm and 63 patients in the placebo arm (50%) who had at least one important protocol deviation. The only protocol deviation category with $\geq 5\%$ higher incidence in the donanemab arm compared to placebo was in the “laboratory assessment criteria” (9.2% vs. 4.0%). These deviations encompass collection of PK and laboratory assessments. The most common category of protocol deviation was for “study procedures criteria.” Review of these deviations did not reveal systemic issues which would affect the interpretation of the study results.

Table of Demographic Characteristics

Table 5 contains information regarding demographic characteristics for the treatment arms in the Full Analysis Set. Demographic characteristics were reasonably balanced across the treatment arms and generally representative of the patient population except for an under-representation of African American and Hispanic patients. There is no reason to expect that efficacy would be different based on race/ethnicity. Overall, 91% of patients were enrolled in the United States.

Table 5: Study AACG Baseline Demographics (Full Analysis Set)

Demographic Parameters	Placebo (N=120) n (%)	Donanemab (N=125) n (%)	Total (N=245) n (%)
Sex			
Male	59 (49%)	61 (49%)	120 (49%)
Female	61 (51%)	64 (51%)	125 (51%)
Age			
Mean years (SD)	75.3 (5.4)	74.9 (5.5)	75.1 (5.5)
Median (years)	76	75	75
Min, max (years)	64, 85	61, 86	61, 86
Age Group			
≤ 64 years	5 (4%)	4 (3%)	9 (4%)
> 65 - < 75 years	43 (36%)	54 (43%)	97 (39%)
≥ 75 years	72 (60%)	67 (54%)	139 (57%)
Race			
White	116 (97%)	116 (93%)	232 (95%)
Black or African American	3 (3%)	5 (4%)	8 (3%)
Asian	1 (<1%)	1 (<1%)	2 (<1%)
American Indian or Alaska Native	0	2 (2%)	2 (<1%)
Native Hawaiian or Other Pacific Islander	0	0	0
Other	0	1 (<1%)	1 (<1%)
Ethnicity			
Hispanic or Latino	3 (2.5%)	4 (3%)	7 (3%)
Not Hispanic or Latino	117 (97.5%)	121 (97%)	238 (97%)
Region			
United States	109 (91%)	115 (92%)	224 (91%)
Rest of the World			
Canada	11 (9%)	10 (8%)	21 (9%)

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Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Table 6 contains a summary of baseline disease characteristics and baseline use of concomitant Alzheimer's disease medications. Disease characteristics are reasonably balanced between the treatment arms and mostly reflect a population of patients who are early in the course of Alzheimer's disease. Interestingly, a formal clinical diagnosis of MCI due to Alzheimer's disease or mild Alzheimer's disease dementia was not required for study entry and some patients were apparently enrolled prior to diagnosis. Overall, the mean baseline scores on the CDR-SB, MMSE, ADAS-Cog 13, and the ADCS-iADL appear to be consistent with a population with mild cognitive impairment and mild to minimal functional impairment, although there are a few outliers who had more marked impairment on these assessments. The percentage of the population who were ApoE ε4 carriers (73%) is consistent with previous reports as is the proportion of patients receiving concomitant cholinesterase inhibitors and/or memantine (68%).

Table 6: Study AACG Disease Characteristics (Full Analysis Set)

Disease Characteristics	Placebo (N=120) n (%)	Donanemab (N=125) n (%)	Total (N=245) n (%)
Laboratory ApoE ε4 Status			
Carrier	88 (73%)	92 (74%)	180 (73%)
Homozygote	26 (22%)	25 (20%)	51 (21%)
Heterozygote	62 (52%)	67 (54%)	129 (53%)
Non-carrier	31 (26%)	33 (26%)	64 (26%)
Undetermined	1 (<1%)	0	1 (<1%)
Number of Years of Formal Education			
Mean years (SD)	15.5 (2.8)	14.6 (2.6)	15.1 (2.7)
Median (years)	16	14	15
Min, Max (years)	11, 24	6, 22	6, 24
Number of Years Since Diagnosis of AD	67	80	147
Mean years (SD)	1.17 (1.45)	1.12 (1.63)	1.14 (1.55)
Median (years)	0.57	0.54	0.55
Min, Max (years)	-0.19, 5.65	-0.15, 10.18	-0.19, 10.18
Concomitant AD medication			
Cholinesterase inhibitors and/or Memantine	80 (67%)	86 (69%)	166 (68%)
Cholinesterase inhibitors	71 (59%)	75 (60%)	146 (60%)
Memantine	27 (23%)	30 (24%)	57 (23%)
Baseline CDR-SB			
Mean (SD)	3.37 (1.70)	3.55 (2.04)	3.46 (1.88)

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Median	3.5	3.5	3.5
Min, Max	0.5, 8.0	0.5, 11.0	0.5, 11.0
Baseline MMSE	115	121	236
<20	6 (5%)	9 (7%)	15 (6%)
≥20 - <27	88 (77%)	88 (73%)	176 (75%)
≥27 - ≤30	21 (18%)	24 (20%)	45 (19%)
Min, Max	16, 29	14, 29	14, 29
Baseline ADAS-Cog 13			
Mean (SD)	27.5 (7.6)	27.7 (7.7)	27.6 (7.6)
Median	27	27	27
Min, Max	5, 47	10, 51	5, 51
Baseline ADCS-iADL			
Mean (SD)	48.6 (7.4)	49.0 (7.2)	48.8 (7.3)
Median	51	51	51
Min, Max	24, 59	22, 59	22, 59
Baseline iADRS			
Mean (SD)	106.1 (13.0)	106.3 (12.7)	106.2 (12.9)
Median	107.5	108.0	108.0
Min, Max	67, 139	60, 130	60, 139

Created by the reviewer using adsl.xpt and sc.xpt.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Compliance to treatment was based on the number of patients receiving an infusion at a given visit. Compliance in the donanemab treatment arm ranged from 94% to 100%, depending on the study visit, whereas placebo compliance was 100% at every visit. Although compliance was high, dose modifications due to adverse events, including ARIA, meant that some patients received fewer than the 19 planned doses. For example, the mean number of infusions in the donanemab treatment arm was 13.4, compared with 15.3 in the placebo arm.

In the donanemab treatment arm, the dose could have been reduced to 700 mg or 0 mg based on amyloid PET results at Weeks 24 and 52 as described earlier. At Week 28 (the first donanemab administration after the Week 24 PET results), 27% of patients in the donanemab treatment arm had their dose reduced to 0 mg and 24% of patients had their dose reduced to 700 mg. By Week 56, a total of 55% of patients in the donanemab treatment arm were administered 0 mg, and 23% were administered 700 mg. At the end of the study, a total of 25% of patients randomized to the donanemab treatment arm were still receiving 1400 mg.

Overall, 11% of study participants started a new concomitant Alzheimer’s disease medication at some point during the study and 5% changed the dose of an existing Alzheimer’s disease medication. The percentages were similar between the placebo and treatment arms.

Efficacy Results – Surrogate Endpoint

Donanemab treatment demonstrated a statistically significant treatment effect on the surrogate endpoint of change from baseline in brain amyloid as measured by ¹⁸F-florbetapir PET and reported as Centiloids at Week 76 (-85.1, p<0.001) (Table 7). The results indicate a time-dependent relationship for reduction of brain amyloid with the donanemab dosing regimen which nears a plateau by Week 52 (Figure 1). The median [25th – 75th percentile] Centiloids value in donanemab treated patients at Week 76 was 12.9 [-0.41 – 30.6]. At the Week 76 assessment, 68% of patients receiving donanemab treatment had Centiloid levels less than 24.1.

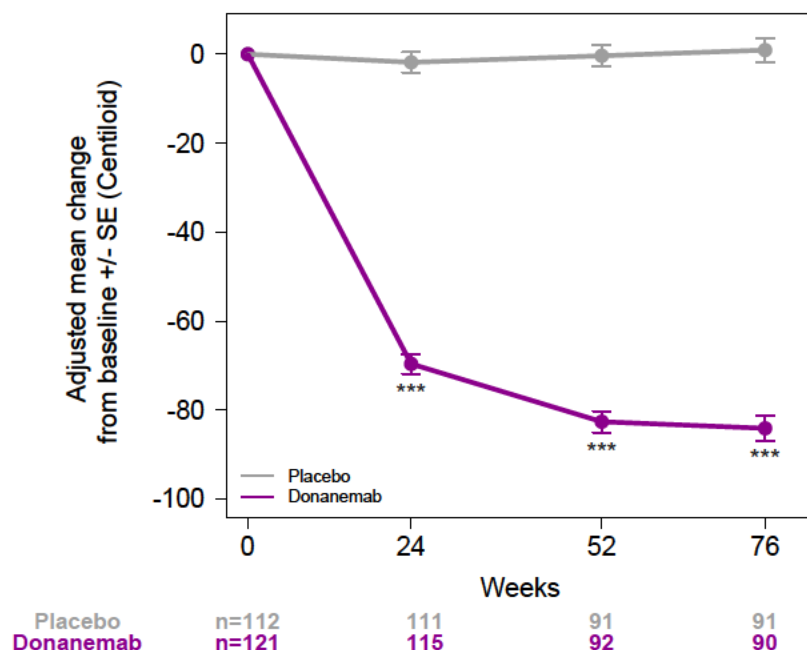
Table 7: Study AACG Surrogate Endpoint Analysis (Centiloids)

	Placebo (N=112)	Donanemab (N=121)
Baseline Centiloid		
n	112	121
Mean (SD)	103.1 (33.8)	107.2 (33.9)
Min, max	38.7, 225.2	41.8, 216.2
Change from Baseline in Centiloid at Week 24		

n	111	115
Least square mean	-1.8	-69.6
Standard error	2.3	2.2
Difference from placebo		-67.8
95% CI for difference		(-74.0, -61.6)
p-value		<0.001
Change from Baseline in Centiloid at Week 52		
n	91	92
Least square mean	-0.35	-82.7
Standard error	2.4	2.4
Difference from placebo		-82.3
95% CI for difference		(-89.0, -75.6)
p-value		<0.001
Change from Baseline in Centiloid at Week 76		
n	91	90
Least square mean	0.9	-84.1
Standard error	2.7	2.7
Difference from placebo		-85.1
95% CI for difference		(-92.7, -77.4)
p-value		<0.001

Source: Table AACG.5.8 in Study AACG CSR

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



Created by the reviewer from Table AACG.5.8 in Study AACG CSR

***p<0.001

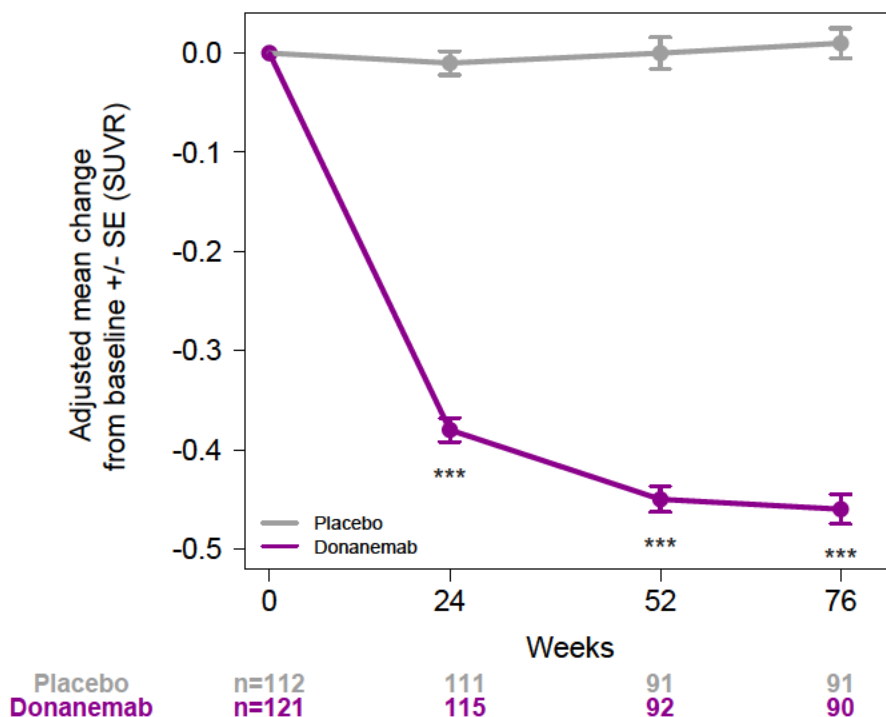
Changes in brain amyloid using SUVR are presented in Table 8 and Figure 2. The results are consistent with those reported for the Centiloid analysis. The change from baseline in brain amyloid at Week 76 in the donanemab arm compared to placebo was -0.46 ($p < 0.001$) and the median [25th – 75th percentile] SUVR value was 1.04 [0.97 – 1.14].

Table 8: Study AACG Surrogate Endpoint Analysis (SUVR)

	Placebo (N=112)	Donanemab (N=121)
Baseline SUVR		
N	112	121
Mean (SD)	1.53 (0.19)	1.55 (0.19)
Min, max	1.18, 2.20	1.20, 2.15
Change from Baseline in SUVR at Week 24		
N	111	115
Least square mean	-0.01	-0.38
Standard error	0.01	0.01
Difference from placebo		-0.37
95% CI for difference		(-0.40, -0.34)
p-value		<0.001
Change from Baseline in SUVR at Week 52		
n	91	92
Least square mean	0.00	-0.45
Standard error	0.01	0.01
Difference from placebo		-0.45
95% CI for difference		(-0.49, -0.41)
p-value		<0.001
Change from Baseline in SUVR at Week 76		
n	91	90
Least square mean	0.01	-0.46
Standard error	0.02	0.02
Difference from placebo		-0.46
95% CI for difference		(-0.51, -0.42)
p-value		<0.001

Source: Table APP 1.1. in Response to Information Request

Figure 2: Study AACG Change from Baseline in Brain Amyloid (SUVR)



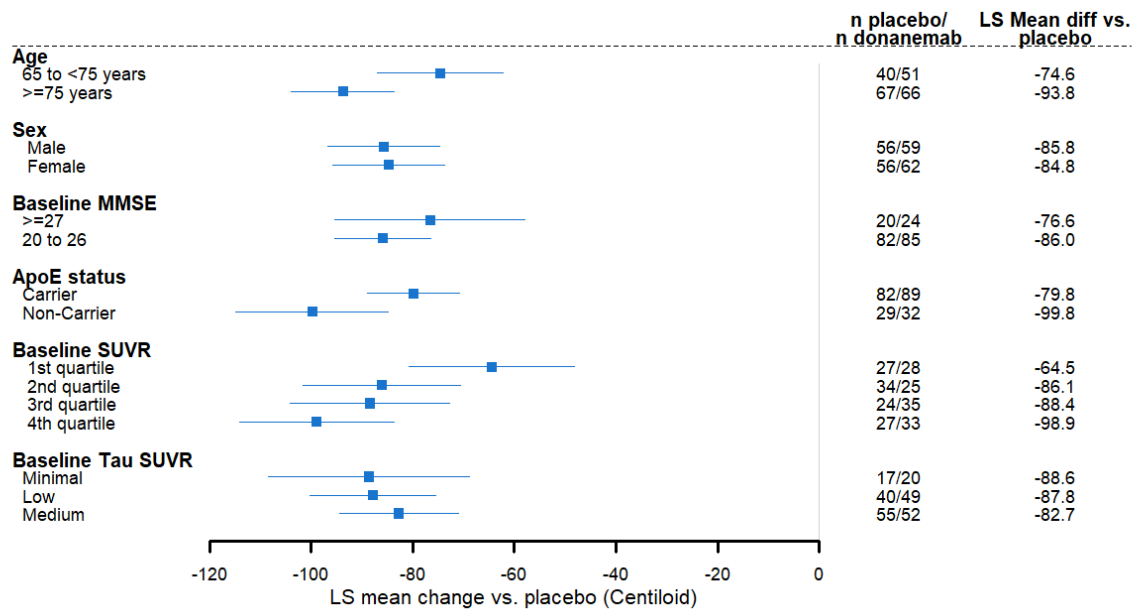
Created by the reviewer from Table APP1.1. in Response to Information Request
***p<0.001

Subgroup Analysis of the Surrogate Endpoint

Subgroup analyses for the surrogate endpoint are summarized in Figure 3 and demonstrate that significant amyloid plaque reduction is observed across patient demographics and disease characteristics. There were too few patients for meaningful subgroup analyses by race or region. PKPD modeling of the relationship between donanemab exposure and amyloid plaque reduction revealed that the time to achieve amyloid plaque levels <11 Centiloids was longer with higher baseline amyloid plaque level. No other factors were found to have a statistically significant impact on the treatment effect. See the clinical pharmacology review for more information.

Given the size of the study, subgroup analyses for clinical endpoints are not presented in this review. Of the pre-defined subgroups listed in the SAP, the statistical review presents one (ApoE ε4 carrier status) to raise uncertainty regarding the impact of amyloid reduction on clinical endpoints because there is no apparent treatment effect on the clinical endpoint in ApoE ε4 non-carriers. Subgroup analyses on clinical endpoints are better suited for the larger confirmatory study.

Figure 3: Study AACG Subgroup Analysis of Amyloid PET Centiloids



Created by reviewer from Tables APP 2.1 to APP 2.6 in Response to Information Request
Note: There were too few patients age <65 years or with baseline MMSE <20 for meaningful results
Note: For baseline tau SUVR: minimal is SUVR <1.10, low is SUVR 1.10 to 1.23, and high is SUVR ≥1.23

Data Quality and Integrity

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

Efficacy Results – Primary Endpoint

The primary efficacy endpoint analysis, change from baseline in iADRS at Week 76, demonstrated a statistically significant treatment effect in the donanemab treatment arm compared to placebo (3.20 [-32%], p=0.042) (Table 9). The treatment effect appears with nominal statistical significance by Week 36 (Figure 4).

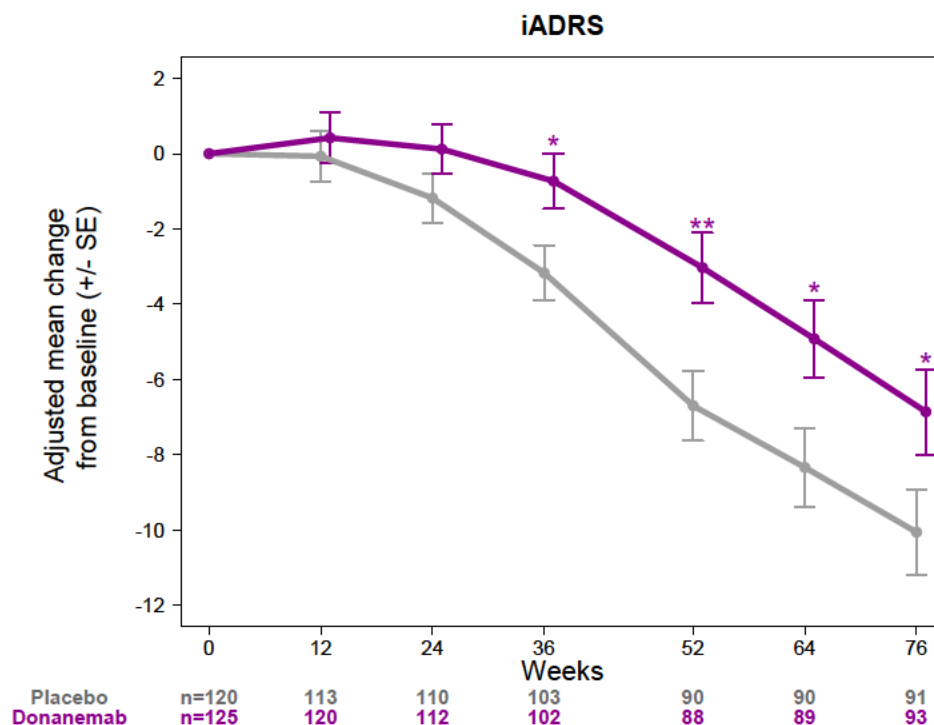
Table 9: Study AACG Primary Endpoint Analysis

	Placebo (N=120)	Donanemab (N=125)
Baseline iADRS		
n	120	125
Mean	106.06	106.30
Change from Baseline in iADRS at Week 76		
n	91	93
Adjusted mean	-10.06	-6.86
Standard error	1.14	1.14

Difference from placebo		3.20
95% CI for difference		(0.12, 6.27)
% difference vs. placebo		-32%
p-value (compared with placebo)		0.042

Source: Table AACG.5.1 in Study AACG CSR

Figure 4: Study AACG Longitudinal Change from Baseline for iADRS



Created by the reviewer from Table AACG.5.1 in Study AACG CSR

*p<0.05

**p<0.01

Efficacy Results – Secondary clinical endpoints

The estimate of the treatment difference between the donanemab and placebo arms for the first secondary endpoint in the hierarchy, CDR-SB at Week 76, numerically favored donanemab, but was not statistically significant (-0.36 [-23%], p=0.14). A summary of the MMRM analysis results for all secondary clinical endpoints at Week 76 is provided in Table 10 and longitudinal results are illustrated in Figure 5. Favorable trends were observed across all secondary endpoints with nominal statistical significance being achieved at one or more timepoints. Overall, these results provide support for the effect observed for the primary endpoint. Specifically, it does not appear that iADRS is solely driven by either component.

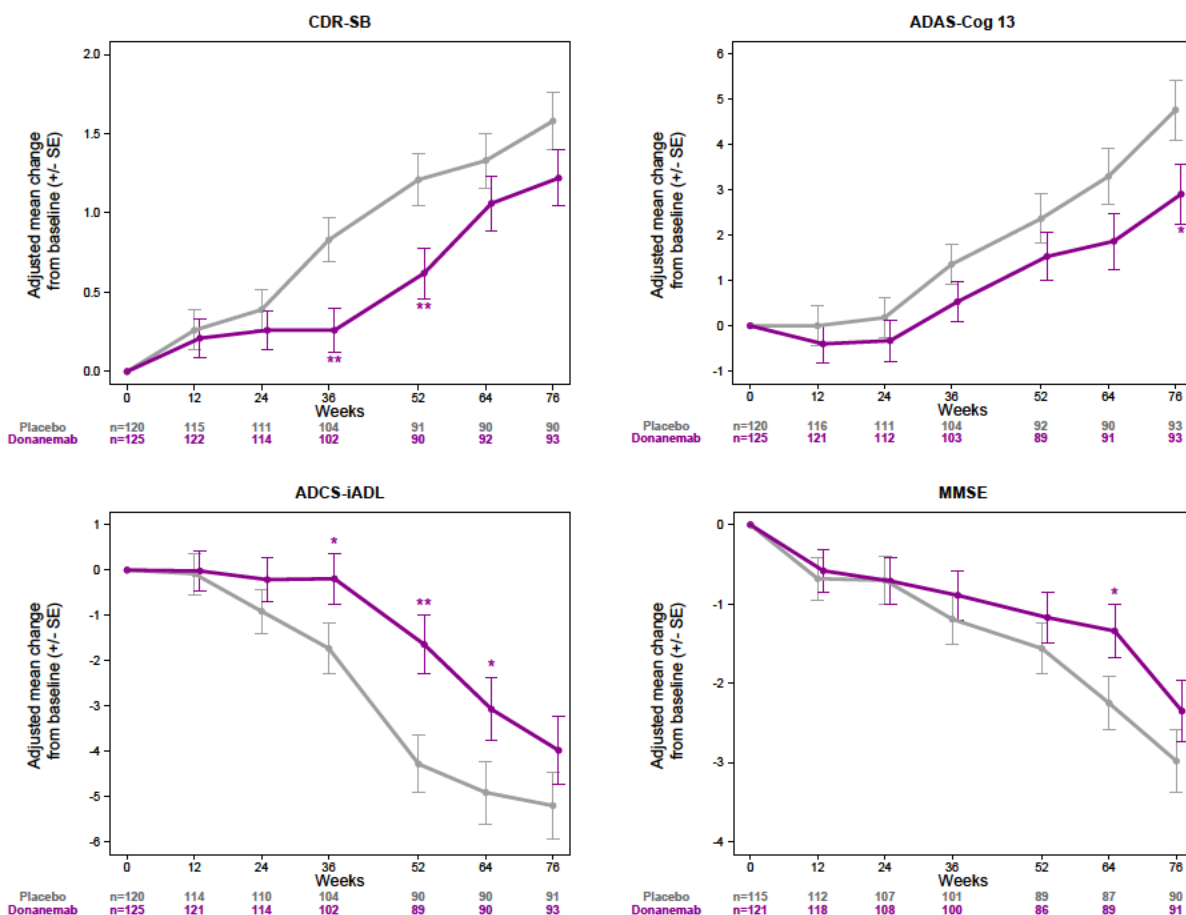
Table 10: Secondary Endpoint Analysis (Week 76)

	Placebo (N=120)	Donanemab (N=125)
Baseline CDR-SB		
N	120	125
Mean	3.37	3.55
Change from Baseline in CDR-SB at Week 76		
N	90	93
Adjusted mean	1.58	1.22
Standard error	0.18	0.18
Difference from placebo		-0.36
95% CI for difference		(-0.83, 0.12)
% difference vs. placebo		23%
p-value (compared with placebo)		0.14
Baseline ADAS-Cog 13		
N	120	125
Mean	27.53	27.68
Change from Baseline in ADAS-Cog 13 at Week 76		
N	93	93
Adjusted mean	4.77	2.91
Standard error	0.66	0.66
Difference from placebo		-1.86
95% CI for difference		(-3.63, -0.09)
% difference vs. placebo		39%
p-value (compared with placebo)		0.040
Baseline ADCS-iADL		
N	120	125
Mean	48.58	48.98
Change from Baseline in ADCS-iADL at Week 76		
N	91	93
Adjusted mean	-5.20	-3.98
Standard error	0.74	0.74
Difference from placebo		1.21
95% CI for difference		(-0.77, 3.20)
% difference vs. placebo		23%
p-value (compared with placebo)		0.230
Baseline MMSE		
N	115	121
Mean	23.77	23.56
Change from Baseline in MMSE at Week 76		
N	90	91
Adjusted mean	-2.98	-2.35
Standard error	0.39	0.39
Difference from placebo		0.64

95% CI for difference		(-0.40, 1.67)
% difference vs. placebo		21%
p-value (compared with placebo)		0.227

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

Figure 5: Study AACG Longitudinal Change from Baseline for Secondary Clinical Endpoints for Placebo and Donanemab Treatment Arms



Created by the reviewer

Source: Tables AACG.5.2, AACG.5.3, AACG.5.4, and AACG.5.5 in Study AACG CSR

*p<0.05

**p<0.01

Efficacy Results – Pharmacodynamic endpoints

Tau PET

The primary prespecified comparisons of change from baseline to Week 76 in global tau load and annualized global tau load computed from the Tau IQ algorithm showed no treatment differences, 0.01 (-0.01, 0.03), $p=0.56$ and 0.00 (-0.1, 0.02), $p=0.60$, respectively. Another prespecified analysis of the overall cortical tau level using a weighted neocortical composite SUVR demonstrated a treatment effect in favor of donanemab, 0.035 (0.008, 0.063), $p=0.0125$ or 34%. Post hoc regional analyses performed for target brain regions suggested a slowing of tau increase for the various regions (Table 11). Subsequent exploratory analyses revealed that this effect was stronger for patients who had reduction of brain amyloid plaque level to less than 24 Centiloids by Week 24 compared to those who did not.

Table 11: Summary of Tau PET Regional Analysis (Week 76)

Region	LS Mean Change from Baseline		Difference from Placebo (95% CI)	% Difference
	Donanemab (N=89)	Placebo (N=84)		
Frontal Lobe	0.0231	0.0589	0.0358 (0.0138, 0.0578)	61%
Occipital Lobe	0.0862	0.1030	0.0168 (-0.0149, 0.0486)	16%
Parietal Lobe	0.0476	0.0887	0.0411 (0.0158, 0.0663)	46%
Lateral Temporal Lobe	0.0644	0.0962	0.0317 (0.0035, 0.0600)	33%

Source: Tables AACG.5.9, AACG.8.22, AACG.8.23, AACG.8.24, and AACG.8.25 in Study AACG CSR

vMRI

Donanemab treatment was associated with a decrease in whole brain volume and an increase in total ventricular volume at Week 76. There was no notable treatment difference in change from baseline in hippocampus volume. Analysis results for prespecified brain regions are provided in Table 12. Given the favorable results on clinical endpoints observed in Study AACG, the clinical relevance of changes to whole brain volumes is unclear. It will be important to collect longer-term data in a larger number of patients to further understand the clinical implications, if any, of these observations.

Table 12: Summary of vMRI Analysis (Week 76)

Region (bilateral)	Baseline (cm ³)		LS Mean Change from Baseline (Week 76)		Difference from Placebo (95% CI)
	Donanemab (N=124)	Placebo (N=119)	Donanemab (N=82)	Placebo (N=83)	
Cortical	364.64	362.51	-11.18	-8.51	-2.67 (-3.92, -1.43)
Entorhinal cortex	2.69	2.64	-0.17	-0.17	0

					(-0.02, 0.02)
Hippocampus	6.17	6.08	-0.22	-0.22	0.01 (-0.03, 0.04)
Inferior parietal lobe	21.21	21.31	-0.53	-0.45	-0.08 (-0.17, 0.01)
Isthmus cingulate	4.14	4.09	-0.15	-0.13	-0.02 (-0.04, 0.00)
Lateral parietal lobe	61.15	61.08	-1.60	-1.26	-0.34 (-0.57, -0.11)
Medial temporal lobe	14.48	14.22	-0.73	-0.72	-0.01 (-0.08, 0.06)
Precuneus	16.15	16.09	-0.71	-0.55	-0.16 (-0.25, -0.07)
Prefrontal lobe	51.25	51.19	-1.50	-1.11	-0.40 (-0.62, -0.17)
Superior temporal lobe	19.51	19.32	-0.73	-0.52	-0.21 (-0.30, -0.12)
Ventricles	50.95	52.43	8.66	6.38	2.28 (1.14, 3.43)
Whole brain	977.34	972.58	-24.53	-19.95	-4.58 (-7.58, -1.59)
Whole temporal lobe	82.90	81.49	-3.52	-2.84	-0.68 (-1.03, -0.33)
White matter	386.76	384.91	-11.03	-8.75	-2.28 (-4.23, -0.33)

Source: Table AACG.8.26 in Study AACG CSR

Plasma Biomarkers

Plasma p-tau 217 was evaluated in 242 patients (119 in the placebo arm and 123 in the donanemab treatment arm). The applicant reports a decrease in plasma p-tau 217 with donanemab treatment with $\log_{10}$ LS mean changes at Week 76 for placebo and donanemab of 0.03 and -0.11, respectively (LS means difference of -0.14, $p < 0.001$). There was a significant correlation between change from baseline in plasma p-tau 217 and percent change in amyloid PET from baseline ($R = 0.484$, $p < 0.0001$).

Plasma glial fibrillary acidic protein (GFAP) was evaluated in 210 patients (104 in the placebo arm and 106 in the donanemab treatment arm). The applicant reports a decrease in GFAP with donanemab treatment with $\log_{10}$ LS mean changes at Week 76 for placebo and donanemab of 0.06 and -0.06, respectively (LS means difference of -0.12, $p < 0.001$). There was a significant correlation between change from baseline in GFAP and percent change in amyloid PET from baseline ($R = 0.453$, $p < 0.0001$).

Treatment effects were not observed for plasma NfL. See the clinical pharmacology review for further consideration of plasma biomarker data.

Dose/Dose Response

A dose-response relationship was not observed because only a single dosing regimen was included in the study. Greater amyloid plaque reduction was associated with higher doses of donanemab in the single- and multiple-ascending dose study (Study AACD). See the clinical pharmacology review for further information, including exposure-response relationships.

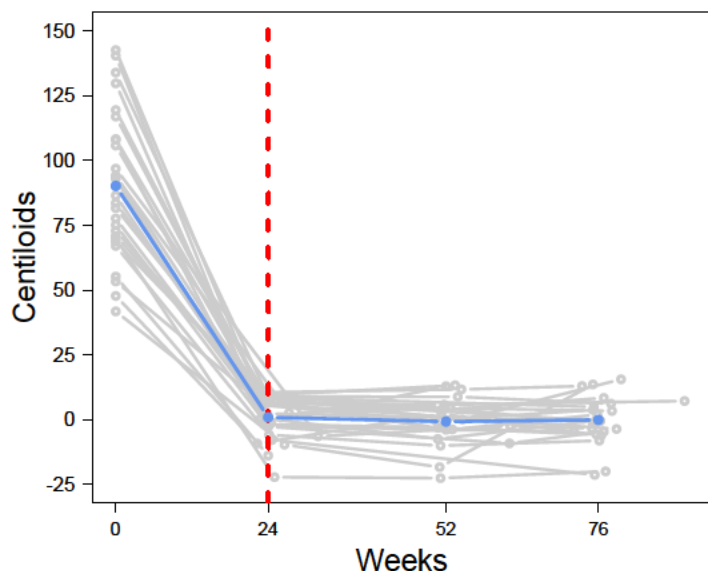
Durability of Response

The reduction in brain amyloid induced by the donanemab dosing regimen was sustained throughout the study (Figure 1). In the absence of a long-term extension, there is limited data to inform the durability of response in patients who may require longer treatment with donanemab 1400 mg to achieve a level of plaque reduction sufficient to stop treatment. It is also noteworthy that nominally statistically significant treatment effects as early as Week 36 for CDR-SB and ADCS-iADL were not sustained at Week 76, although it is also important to exercise caution in interpreting trends in clinical endpoints in Study AACG. Ultimately, the larger confirmatory study will more fully inform the durability of response.

Persistence of Effect

The effect of donanemab after treatment is stopped is partially informed by data in patients who met criteria to have their dose reduced to placebo during the study. The individual profiles for patients who had Centiloid values less than 11 at Week 24 and therefore had their subsequent doses reduced to placebo are plotted in Figure 6. In these patients there does not appear to be any substantial reaccumulation over this limited period of time. It is worth noting, however, the relatively short off-treatment period and the fact that the donanemab dose administered at Week 24 continues to exert a pharmacodynamic effect during the beginning of the off-treatment period. Although amyloid PET is an important marker, it is also possible that other unmeasured biomarkers may indicate that the pathological process of amyloid accumulation is occurring in the absence of treatment. Given these limitations, it is challenging to provide data-driven recommendations regarding the possibility of re-initiation of dosing.

Figure 6: Individual Amyloid Plaque Profiles (Centiloid) in Patients who Met Criteria to Have Donanemab Treatment Stopped after Week 24



Created by the reviewer using adpet1.xpt
Dashed red line represents stoppage of donanemab dosing
Blue solid line represents the mean values

Additional Analyses Conducted on the Individual Trial

Correlation between Amyloid PET and Clinical Endpoints

The correlation between the change from baseline on amyloid PET and the change from baseline in clinical endpoints was explored separately in the placebo and donanemab treatment arms at the individual level. No statistically significant correlations were observed. It is not surprising that despite a treatment effect, there is not a tight correlation between reduction in brain A β plaque levels and clinical endpoints at the individual level. It has been recognized that brain A β burden is not well correlated with disease progression and there is not an a priori expectation of precisely how reduction in A β burden would relate to changes on clinical scales. Furthermore, when individual data from one dose level is used to quantify the relationship between two endpoints, it is challenging to correctly adjust the imbalances of multiple confounders due to potential nonlinear and complex relationships. Group-level correlation is not possible because only a single dose was included in the study.

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

7. Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

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

7.2. Additional Efficacy Considerations

7.2.1. Considerations on Benefit in the Postmarket Setting

The population enrolled in Study AACG did not include patients at either end of the Alzheimer's disease continuum and there is some uncertainty with respect to the generalizability of benefit across the entire spectrum of Alzheimer's disease. There is a general expectation, however, that initiating treatment with donanemab earlier in the disease may provide the best opportunity to delay or halt the pathophysiological processes that lead to the clinical deficits of Alzheimer's disease. The ongoing study (Study AACM) of donanemab in individuals at risk for cognitive and functional decline of Alzheimer's disease should shed light on potential benefit in this population. Intervention with donanemab later in the disease may be expected to provide less benefit, as downstream pathological processes may dominate. The application does not contain clinical data to directly assess the effectiveness of donanemab at either end of the disease continuum. On the other hand, Alzheimer's disease is defined in part by the presence of amyloid pathology, and the pharmacodynamic effect of donanemab on reduction of brain amyloid plaque should occur across the disease continuum, providing the potential for clinical benefit.

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

7.3. Integrated Assessment of Effectiveness

The effect of donanemab on brain amyloid plaque demonstrated in Study AACG, an adequate and well-controlled study, was robust and persuasive and meets the statutory standard for substantial evidence of effectiveness to support accelerated approval. The proposed dosing regimen demonstrated a reduction in brain amyloid plaque from 107.2 Centiloids at baseline to

23.1 Centiloids at Week 76 with a statistically significant difference from placebo of -85.1 Centiloids ($p < 0.001$). The magnitude of reduction is consistent with the observed reductions that supported the accelerated approvals of aducanumab and lecanemab.

The reduction of brain amyloid was highly persuasive. As observed in the placebo arm of Study AACG, amyloid plaque does not spontaneously disappear in patients with Alzheimer's disease. The reduction observed in the donanemab treatment arm is thus incompatible with variability or chance. Also, donanemab has demonstrated dose- and concentration-response relationships across doses in earlier single- and multiple ascending dose studies. The effects on amyloid are persuasive and consistent across subgroups, supporting the ability of Study AACG to be considered a single adequate and well-controlled trial that is capable of providing substantial evidence of effectiveness.

The clinical endpoint results from Study AACG provide context for the amyloid reduction observed in the study and inform the reasonable likelihood of the reduction in brain amyloid plaque to predict clinical benefit. Importantly, the prespecified primary endpoint in Study AACG was positive. Despite not reaching statistical significance according to the prespecified hierarchy, the estimates of the treatment effect at Week 76 across secondary clinical endpoints are consistent with a modest reduction of clinical decline. Importantly, a similar degree of reduction (approximately 20% to 40%) in the decline of clinical endpoints has been observed in other studies in which brain amyloid was reduced to a similar extent. This reduction corresponds to a delay in progression of several months over the 18 months of the study. Patients and caregivers have clearly expressed that a delay of several months at this stage of the disease is clinically important.

It is noted that the applicant did not require a formal clinical diagnosis of mild cognitive impairment due to Alzheimer's disease or mild Alzheimer's disease dementia for enrollment in Study AACG. Instead, patients were enrolled based on Alzheimer's disease pathology and presence of clinical symptoms and objective evidence of cognitive impairment with scoring in the mild range. These criteria are generally consistent with an operationalization of the 2018 NIA-AA Research Framework for Alzheimer's disease (Jack et al. 2018) for mild cognitive impairment or mild dementia due to Alzheimer's disease. Overall, the mean baseline scores on the CDR-SB, MMSE, ADAS-Cog 13, and the ADCS-iADL appear to be consistent with a study population with mild cognitive impairment and mild to minimal functional impairment, although there are a small number of outliers who had more marked impairment on these assessments. For this reason, it is appropriate for the indication statement to refer to mild cognitive impairment due to Alzheimer's disease or mild Alzheimer's disease dementia.

The evidence provided in the submission clearly meets the criteria for accelerated approval. Alzheimer's disease is a serious and life-threatening condition with a tremendous unmet medical need. Donanemab targets the underlying pathology of the disease and may provide a

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Kevin Krudys, PhD
BLA 761248
Kisunla (donanemab)

meaningful therapeutic benefit over existing treatment. Note that aducanumab and lecanemab have received accelerated approval and thus are not considered available treatment for this purpose. The Division has determined that an effect on brain amyloid plaque is reasonably likely to predict benefit. The data provided in the donanemab program and from topline results from other studies support this conclusion. Finally, donanemab has demonstrated a robust and statistically significant effect on reduction of brain amyloid plaque.

8. Review of Safety

Please see the separate safety review by Dr. Branagan.

9. Advisory Committee Meeting and Other External Consultations

An Advisory Committee Meeting was not deemed necessary for this submission.

10. Labeling Recommendations

10.1. Prescription Drug Labeling

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

10.2. Nonprescription Drug Labeling

Not applicable.

11. Risk Evaluation and Mitigation Strategies (REMS)

Please see the separate safety review by Dr. Branagan for consideration regarding a REMS.

12. Postmarketing Requirements and Commitments

In order to verify the clinical benefit of donanemab, the applicant will be required to conduct a randomized, controlled trial to evaluate the efficacy of donanemab compared to an appropriate

control for the treatment of Alzheimer's disease. The trial should be of a sufficient duration to observe changes on an acceptable endpoint in the patient population enrolled in the trial. The ongoing Study AACI is intended to address this requirement.

13. Appendices

13.1. References

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13.2. Financial Disclosure

Clinical Review
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Kisunla (donanemab)

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

Was a list of clinical investigators provided:	Yes ☒	No ☐
Total number of investigators identified: <u><750</u>		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>5</u>		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: <u>5</u> Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>0</u>		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

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KEVIN M KRUDYS
01/17/2023 11:19:35 PM

Clinical Review
 Natalie Branagan, MD
 BLA 761248
 Kisunla/donanemab

CLINICAL REVIEW

Application Type	BLA
Application Number(s)	761248
Priority or Standard	Priority
Submit Date(s)	May 18, 2022
Received Date(s)	May 18, 2022
PDUFA Goal Date	January 18, 2023
Division/Office	DN 1/ON
Reviewer Name(s)	Natalie Branagan, MD
Review Completion Date	January 17, 2023
Established/Proper Name	Donanemab
(Proposed) Trade Name	Kisunla
Applicant	Eli Lilly and Company
Dosage Form(s)	Injection, intravenous
Applicant Proposed Dosing Regimen(s)	700 mg as an intravenous infusion over four weeks for the first 3 doses, followed by 1400 mg every four weeks, until brain amyloid plaque is cleared.
Applicant Proposed Indication(s)/Population(s)	(b) (4)
Recommendation on Regulatory Action	The safety database does not fulfill minimum ICH guidance for exposure of at least 100 patients for 12 months at the proposed dose for drugs intended for long-term use. Therefore, the safety database is insufficient to adequately characterize the long-term safety of donanemab in the treatment of Alzheimer's disease.
Recommended Indication(s)/Population(s) (if applicable)	

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Glossary

AC	advisory committee
AD	Alzheimer's disease
AE	adverse event
AR	adverse reaction
ARIA	Amyloid related imaging abnormality
ARIA-E	Amyloid related imaging abnormality-edema
ARIA-H	Amyloid related imaging abnormality-microhemorrhages and hemosiderin deposition
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Council for Harmonization
IND	Investigational New Drug Application
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat

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MedDRA	Medical Dictionary for Regulatory Activities
MCI	Mild cognitive impairment
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information or package insert
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

1. Executive Summary

1.1. Product Introduction

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

1.2. Conclusions on the Substantial Evidence of Effectiveness

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

1.3. Benefit-Risk Assessment

[Please refer to the Summary Memo.](#)

Benefit-Risk Dimensions

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1.4. Patient Experience Data

Please refer to the review of clinical efficacy by Dr. Kevin Krudys.

2. Therapeutic Context

2.1. Analysis of Condition

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

2.2. Analysis of Current Treatment Options

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

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

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

3.2. Summary of Presubmission/Submission Regulatory Activity

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

3.3. Foreign Regulatory Actions and Marketing History

There is no foreign marketing experience.

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

4.1. Office of Scientific Investigations (OSI)

The reader is referred to the OSI review.

4.2. Product Quality

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The reader is referred to the Product Quality review.

4.3. Clinical Microbiology

Not applicable.

4.4. Nonclinical Pharmacology/Toxicology

The reader is referred to the Nonclinical Pharmacology review.

4.5. Clinical Pharmacology

The reader is referred to the Clinical Pharmacology review.

4.6. Devices and Companion Diagnostic Issues

Not applicable.

4.7. Consumer Study Reviews

Not applicable.

5. Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

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

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5.2. Review Strategy

The clinical review of BLA 761248 is divided into a review of clinical efficacy (by Dr. Kevin Krudys) and this review of clinical safety. Information submitted as part of BLA 761248 and published literature are discussed in this review. I will primarily present analysis conducted by myself. The primary safety review presented here will focus on Study AACG to reflect the safety in the study that is the primary source of evidence of effectiveness. Studies AACH Part B, AACI Safety Addendum, and AACN-Dona Cohort will provide supportive information.

6. Review of Relevant Individual Trials Used to Support Efficacy

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

7. Integrated Review of Effectiveness

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

8. Review of Safety

8.1. Safety Review Approach

The safety population was defined as all patients who were randomized and received at least one dose of study drug.

The key studies analyzed for the clinical review of safety were comprised of a placebo-controlled study and three open-label studies. The table below contains the key studies analyzed for the clinical review of safety as well as a Phase 1 study that contributed towards exposure calculations and an ongoing placebo-controlled study, whose blinded data is included in this submission.

Table 1. Studies Supporting Safety

Study	Primary Objective	Type of Study	Dose in Safety Population
AACD, Part C	Assess the safety, tolerability, pharmacokinetic, and	Phase 1b randomized within cohort, placebo-	Part C: Chronic dose vs Placebo with 12-week follow-up Placebo (5) Cohort 6: 10 mg/kg IV q 4 weeks for

Study	Primary Objective	Type of Study	Dose in Safety Population
	pharmacodynamic of single and multiple intravenous doses of donanemab in participants with MCI due to AD or mild to moderate AD	controlled, double-blind, parallel-group study	up to 72 weeks (8) Cohort 7: 20 mg/kg IV q 4 weeks for up to 72 weeks (10)
AACG	Evaluate the safety and efficacy of donanemab in patients with early symptomatic AD with presence of intermediate brain tau burden per flortaucipir PET in participants with early symptomatic AD	Phase 2 randomized, double-blind, placebo-controlled study	Placebo (125) Donanemab-M: donanemab 700 mg IV infusion q 4 weeks for three doses, then 1400 mg IV infusion q 4 weeks for up to 72 weeks (131) Donanemab-C: donanemab 700 mg IV infusion q 4 weeks for three doses, then 1400 mg IV infusion q 4 weeks for up to 72 weeks in combination with BACE1 inhibitor LY3202626 (15) Treatment duration: 72 weeks Follow-up: 52 weeks At Weeks 24 or 52, the donanemab dose could be reduced to 700 mg or the participant could be switched to placebo based on amyloid plaque reduction measured by florbetapir PET scan.
AACH Part B (ongoing)	Evaluate the safety, tolerability, and efficacy of donanemab in participants with early symptomatic AD	Phase 2 open-label, follow-on study for participants who received placebo in the originating trial	Donanemab 700 mg IV infusion q 4 weeks for three doses, then 1400 mg IV infusion q 4 weeks for up to 72 weeks (45) Treatment duration: 36 or 48 weeks Follow-up: up to 24 weeks At Week 36, donanemab could be stopped based on amyloid plaque reduction measured by florbetapir PET

Study	Primary Objective	Type of Study	Dose in Safety Population
			scan.
AACI main study (ongoing)	Assess the safety, tolerability, and efficacy of donanemab in early symptomatic AD with the presence of brain tau pathology and to assess whether removal of existing amyloid plaque can slow progression of AD.	Phase 3, multicenter, randomized, double blind, placebo-controlled study	Donanemab 700 mg IV infusion q 4 weeks for three doses followed by 1400 mg IV infusion q 4 weeks, or placebo Treatment duration: up to 150 weeks At Weeks 24, 52, 76, 102, or 130, donanemab could be switched to placebo based on amyloid plaque reduction measured by florbetapir PET scan. Blinded safety data is included in this submission
AACI Safety Addendum (ongoing)	Collect open-label exposure and safety data in participants with early symptomatic AD who have proof of amyloid pathology and receive donanemab	Phase 3, open-label study	Donanemab 700 mg IV infusion q 4 weeks for three doses, then 1400 mg IV infusion q 4 weeks for up to 72 weeks (1047) Treatment duration: 72 weeks Follow-up: up to 44 weeks At Weeks 24 or 52, donanemab could be stopped based on amyloid plaque reduction measured by florbetapir PET scan.
AACN-Dona Cohort (ongoing)	Evaluate the superiority of donanemab to aducanumab in participants with early symptomatic AD	Phase 3, open-label, head-to-head study	Donanemab 700 mg IV infusion q 4 weeks for three doses, then 1400 mg IV infusion q 4 weeks for up to 72 weeks (70) Treatment duration: 76 weeks Follow-up: up to 44 weeks At Weeks 24 or 52, donanemab could

Study	Primary Objective	Type of Study	Dose in Safety Population
			be stopped based on amyloid plaque reduction measured by florbetapir PET scan.

AD: Alzheimer's disease, MCI: mild cognitive impairment

Study AACG, the proposed primary source for evidence of effectiveness, was the source for placebo-controlled safety analyses, and the results for this study are presented individually. The three open-label studies, AACH Part B, AACI Safety Addendum, and AACN-Dona Cohort, were pooled with donanemab-treated participants from Study AACG to create an all-donanemab-treated pool, which allows for analysis of adverse events occurring with exposure to donanemab for up to 12 months.

Study AACG was a randomized, double-blind, placebo-controlled study of donanemab in participants with mild cognitive impairment due to Alzheimer's disease and mild Alzheimer's dementia. The study was comprised of a 9-week screening period, an up to 72-week treatment period with final evaluations occurring 4 weeks later at Week 76, and a 48-week follow-up period. Participants were randomized to either donanemab 700 mg intravenously for the first three doses, then 1400 mg every four weeks for up to 72 weeks or to placebo intravenously every four weeks for up to 72 weeks.

In Study AACG, donanemab doses could be modified based on amyloid plaque reduction measured by florbetapir PET imaging or by the development of ARIA-E. Depending on the degree of amyloid plaque reduction noted at Week 24 or Week 52, donanemab doses could be reduced from 1400 mg to 700 mg or the participant could be switched to placebo. The reader is referred to the [Appendix](#) for further details on dose modifications related to ARIA in Study AACG.

The open-label studies differed from Study AACG in that the donanemab dose was not reduced to 700 mg based on amyloid plaque reduction criteria or the development of ARIA-E. In participants who met dose reduction criteria for amyloid plaque reduction, donanemab was discontinued. The reader is referred to the [Appendix](#) for further details on dose modifications related to ARIA in the open-label studies.

This submission also contains blinded safety data submitted by the sponsor for the ongoing placebo-controlled part of the main study of AACI. In the pre-BLA meeting package dated July 30, 2021, the sponsor proposed to unblind data from the placebo-controlled portion of Study AACI. In pre-BLA meeting minutes dated October 7, 2021, the Division noted that unblinding of data from a clinical trial would raise concerns about the impact on the study's integrity. In an

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email communication dated March 4, 2022, the sponsor proposed to submit blinded data for the placebo-controlled period of Study AACI in response to the Division's communications.

Analysis of Adverse Events

The sponsor analyzed adverse events using two methods.

In the first analysis method, the sponsor included adverse events occurring on the date of the first dose of study drug through the date of the last dose of study drug + 57 days (where 57 days represents approximately five times the half-life of the drug). For participants randomized to the donanemab arm, the last dose of study drug is the last dose of donanemab.

Reviewer comment: This method of analysis potentially introduces bias caused by observing AEs occurring in observation periods of unequal duration. Based on criteria outlined by study protocol as reasons for treatment discontinuation, participants experiencing adverse events such as ARIA and infusion reactions were more likely to discontinue treatment compared to participants who did not experience ARIA and infusion reactions, thus resulting in shorter periods of observation.

In the second analysis method, adverse events were analyzed based on a treatment policy approach. In Study AACG, the sponsor included adverse events occurring within the 76-week placebo-controlled treatment period. In the open-label studies AACH Part B, AACI Safety Addendum, and AACN Dona-Cohort, the sponsor included adverse events occurring during the treatment period (up to 76 weeks) and during the follow up period (up to 48 weeks).

Reviewer comment: Analyses using this method results in comparison of adverse events occurring over equal lengths of observation within each study. In Study AACG, this method does not capture adverse events occurring in the follow-up period that are within five times the half-life of the last dose of donanemab.

For the purpose of this review, adverse events were analyzed based on treatment period plus 57 days (~ 5 times the half-life of donanemab). In Study AACG, this method allows comparison of adverse events occurring in observations periods of similar duration in the active drug and placebo arms and includes AEs occurring within five times the half-life of the drug.

The sponsor analyzed safety results from Study AACD separately from the Phase 2 and 3 studies. Overall, the reviewer found this approach acceptable as participants in Study AACD had different dosing regimens.

Participants exposure to donanemab in Study AACD contributed towards the sponsor's calculations of 6- and 12-months donanemab exposures for the safety database. The reviewer

found this approach acceptable as doses at the 20 mg/kg weight approximated the proposed labeled dose.

Study AACC, a Phase 1 single and multiple-dose dose-escalation study, is not included among the key studies for this safety review as the maximum donanemab dose participants received was 10 mg/kg and is expected to result in lower exposures compared to exposures of participants in Phase 2 and 3 studies.

Amyloid related imaging abnormalities (ARIA) and hypersensitivity reactions are topics of special interest for the safety review of donanemab based on the safety profile of aducanumab, the first amyloid-directed monoclonal antibody drug, approved in June 2021 for the treatment of Alzheimer's disease.¹

Infusion related reactions and immunogenicity are also topics of special interest for this review, based on the observation of infusion related reactions occurring in Phase 1 studies with donanemab.

8.2. Review of the Safety Database

¹ Aduhelm. Labeling-Prescribing Information. Drugs@fda.gov. Action date April 29, 2022. Accessed July 15, 2022.

8.2.1. Overall Exposure

Overall, the sponsor did not meet ICH guidelines of at least 100 patients exposed to the highest clinically relevant doses (700 mg every 4 weeks for 3 doses followed by 1400 mg every 4 weeks) for one year, but did meet ICH guidelines of at least 300 patients for six months. At the time of the 90-Day Safety Update, 49 participants were exposed for 12 months and 827 were exposed for 6 months. However, if considered using the protocol-designed approach (referred to as treatment policy approach) that allowed for reduction in dose or change to placebo based on amyloid plaque reduction, 100 patients were exposed for 12 months. Both approaches are considered in the sections that follow.

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

The following table indicates the safety population across the clinical program at the time of the 90-Day Safety Update and includes participants who received subcutaneous dosing. Of note, participants who received placebo in Study AACG and crossed-over to receive donanemab in follow-on Study AACH were not counted twice in the table. The total number of participants exposed to monotherapy with donanemab in Study AACG is 131.

Table 2. Safety Population, Size and Denominators after the 90-Day Safety Update

Safety Database for the Study Drug ¹ Individuals exposed to any treatment in this development program for the indication under review N=1513 (N is the sum of all available numbers from the columns below)		
Clinical Trial Groups	Donanemab Drug (n=1416)	Placebo (n=97)
Healthy volunteers	6	0
Controlled trials conducted for this indication ²	237	97
All other trials conducted for this	1173	n/a

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indication ³		

¹ *Study drug* means the drug being considered for approval.

² Includes 8 participants from Study AACC who were dosed subcutaneously with donanemab

³ To avoid double-counting participants, 55 participants who received placebo in Study AACC and were then switched to donanemab in the follow-on Study AACH were not included in the total for placebo.

Duration of exposure to study drug was calculated based on the proposed dosing of donanemab, which is 700 mg every four weeks for the first three doses, followed by 1400 mg every four weeks. In Study AACC, dosing differed from the proposed dose in that participants could have the dose lowered from 1400 mg to 700 mg or be switched to placebo based on meeting criteria for amyloid plaque reduction or based on the development of ARIA-E.

The Sponsor stated in the clinical study report for AACC that approximately 27% of donanemab-treated participants at Week 24, and 55% at Week 52, had sufficient lowering of the amyloid plaque level to switch to placebo at their next infusion visit. The following table, from the clinical study report, shows exposure to donanemab 700 mg, 1400 mg, or placebo over time in donanemab-treated participants.

Figure 1. Exposure in Donanemab-Treated Participants By Week in Study AACG

Table AACG.4.5. Donanemab-M Dose Distribution over Time

TIME (weeks)	0 mg	700 mg	1400 mg
0	0	100% (131/131)	0
4	0	100% (127/127)	0
8	0	100% (121/121)	0
12	0	2% (2/107)	98% (105/107)
16	0	5% (5/107)	95% (102/107)
20	0	9% (9/102)	91% (93/102)
24	0	10% (10/101)	89% (90/101)*
28	27% (26/95)	24% (23/95)	48% (46/95)
32	28% (26/92)	24% (22/92)	48% (44/92)
36	28% (24/87)	24% (21/87)	48% (42/87)
40	27% (22/81)	25% (20/81)	48% (39/81)
44	29% (22/77)	25% (19/77)	47% (36/77)
48	29% (23/78)	26% (20/78)	45% (35/78)
52	28% (20/71)	25% (18/71)	46% (33/71)
56	55% (41/75)	21% (16/75)	24% (18/75)
60	52% (38/73)	23% (17/73)	25% (18/73)
64	51% (39/76)	25% (19/76)	24% (18/76)
68	53% (41/77)	22% (17/77)	25% (19/77)
72	52% (40/77)	23% (18/77)	25% (19/77)**

* One participant had 2800 mg (2×1400 mg) dispensed from the pharmacy but only received 1 infusion of 1400 mg.

** There were 5 participants who missed infusions at Week 72 but remained in the study and completed final study assessments (Visit 21) and were considered treatment completers.

The above figure was taken from the CSR for AACG submitted by the sponsor on May 18, 2022 (page 45).

In order to calculate exposure based on the proposed dose, this reviewer included participants in exposure calculations if no more than 3 of the infusions that contributed to exposure totals were at the 700 mg dose, to account for the first three doses of donanemab that were at the 700 mg dose.

At the time of the 90-Day Safety Update (data cutoff of June 16, 2022, for AACH, and May 20, 2022, for AACN and AACI), 1408 healthy volunteers and participants with Alzheimer's disease had been exposed to at least one dose of donanemab intravenously in Studies AACC, AACD, AACG, and the open-label studies AACH Part B, AACI Safety Addendum, and AACN-Dona Cohort. Excluding six healthy volunteers from Study AACC, the total number of patients with Alzheimer's disease exposed to donanemab intravenously was 1402.

The following table shows duration of exposure at the time of the 90-Day Safety Update, based

on three 700 mg-doses of donanemab and followed by 1400 mg-doses. This reviewer included participants who had no more than three 700 mg-doses at any timepoint.

Table 3. Duration of Exposure Based on Donanemab Infusions in the All-Donanemab Pool and in Study AACD at the 90-Day Safety Update

Studies	Number of participants exposed		
	6-mo	9-mo	12-mo
AACG	106	47	41
Initial submission for pooled Studies AACH Part B, AACI Safety Addendum and AACN Dona Cohort	505	3	0
90-Day Safety Exposure Update for pooled Studies AACH Part B, AACI Safety Addendum and AACN Dona Cohort	209	37	3
AACD ^a	7	6	5
Total	827	93	49

The reviewer calculated duration of exposure based on number of donanemab infusions. Participants were included in exposure calculations if no more than 3 of the infusions that contributed to exposure at donanemab 1400 mg doses were at the 700 mg dose. The reviewer created this using the ISS ADEX dataset submitted 8.17.22, which contains data for studies AACG, AACH, AACI, and AACN.

^aIn Study AACD, participants received weight-based dosing. Participants who received 20 mg/kg were included in exposure calculations.

At the time of the 90-Day Safety Update, the all-donanemab pool contained 1,304 participants. This number differs from the sponsor's all-donanemab pool (n=1319) as noted in the 90-Day Safety update as the sponsor's pool includes 15 participants who received donanemab-C in Study AACG.

The following table, which includes 6- and 12-month exposure data included in labeling for donanemab, shows the number of participants exposed to donanemab infusions at the 700 mg or 1400 mg dose in the all-donanemab pool at the time of the 90-Day Safety Update. The safety database includes time participants were exposed to donanemab 1400 mg or 700 mg and does not include time participants were exposed to placebo.

Table 4. Duration of Exposure Based on 700 mg and 1400 mg Doses of Donanemab Infusions in the All-Donanemab Pool after the 90-Day Safety Update.

6-mo	9-mo	12-mo
876	112	67

The reviewer created this table using the IDB ADEX 90Day Safety Update, EXDOSE = 700 and 1400.

The following table shows the number of participants in the all-donanemab pool at the time of

the 90-Day Safety Update with 6, 9, and 12 months of infusions, noted in the sponsor's submission as the Treatment Policy Approach, which includes participants in Study AACG who had dose reductions to donanemab 700 mg or were switched to placebo.

Table 5. Duration of Exposure Based on Treatment Policy Approach for the All-Donanemab Pool after the 90-Day Safety Update.

Studies	Number of Participants Exposed to the Study Drug		
	6-mo	9-mo	12-mo
AACG	113	104	97
AACH Part B	28	16	3
AACI Safety Addendum	707	25	0
AACN Dona Cohort	29	0	0
Total	877	145	100

The reviewer created this table using the IDB ADEX 90Day Safety Update, EXDOSFRM = infusion or IV bag, EXDOSE 6

In an email communication dated March 4, 2022, the sponsor proposed to create an all-donanemab-treated pool by pooling the three open-label studies, AACH Part B, AACI Safety Addendum, and AACN-Dona Cohort, with donanemab-treated participants from Study AACG, which includes 15 participants exposed to combination therapy with donanemab and LY3202626, a β -site amyloid precursor protein cleaving enzyme 1 (BACE1) inhibitor (referred to as donanemab-C). The total number of participants in the sponsor's all-donanemab pool is 1308.

Given the potential difference in safety profiles with combination therapy, the Division does not agree with the sponsor's pooling strategy that includes patients on the combined donanemab and LY3202626 regimen. Safety results for the 15 participants exposed to combination therapy with donanemab and LY3202626 will be summarized separately. After excluding these 15 participants, the all-donanemab pool contains 1,293 participants.

8.2.2. Relevant characteristics of the safety population:

Overall, lower frequencies of female participants, participants of a minority race and ethnicity, and age over 85 years were observed in Study AACG compared to expected frequencies in the U.S. population with Alzheimer's disease. Baseline demographics were similar between donanemab and placebo arms in Study AACG. The safety profile of donanemab in patients with more advanced stages of AD is unknown. The population enrolled in the key studies for safety were identified as having MCI or mild AD, and treatment with donanemab was discontinued after achieving amyloid plaque reduction criteria.

The sponsor notes that participants were enrolled in Study AACG based on pathological staging

of Alzheimer's disease rather than phenotypic staging.² Participants had to have both elevated amyloid measured by positron emission tomography (PET) and presence of tau pathology measured by flortaucipir PET in combination with a mini mental status exam score of 20 to 28. Participants also had to have gradual and progressive change in memory function reported by the participant or informant for ≥ 6 months and be between 60 to 85 years of age.

The reader is referred to the clinical review of efficacy by Dr. Kevin Krudys for an assessment of the adequacy of enrollment criteria used to identify patients with Alzheimer's disease and MCI or mild dementia in the clinical program.

Participants were excluded if they met any of the following criteria: history of epilepsy or recurrent seizures; serious or unstable illness including cardiovascular, hepatic, renal, gastroenterologic, respiratory, endocrinologic, neurologic, psychiatric, immunologic, or hematologic condition; history of long QT syndrome; history of clinically significant multiple or severe drug allergies, or severe posttreatment hypersensitivity reactions; or had a centrally read MRI demonstrating presence of ARIA-E, > 4 cerebral microhemorrhages, more than 1 area of superficial siderosis, any intracerebral hemorrhage, or severe white matter disease. Participants were allowed to use approved medications for Alzheimer's disease concomitantly, if doses had been stable in the preceding two months before the first day of study drug administration. There were no exclusion criteria related to antithrombotics use in Study AACG.

Studies AACH Part B, AACI Safety Addendum, and AACN-Dona Cohort had similar inclusion criteria related to change in memory and MMSE score as compared to AACG. Study AACN enrolled subjects between the age of 50 to 85 years of age inclusive.

Studies AACI Safety Addendum, and AACN-Dona Cohort had similar exclusion criteria as Study AACG including presence of ARIA-E, > 4 cerebral microhemorrhages, more than 1 area of superficial siderosis, any intracerebral hemorrhage, or severe white matter disease at screening.

There were no exclusion criteria related to antithrombotic use in Studies AACH and AACI. In Study AACN, patients were excluded if they were on anticoagulants or antiplatelets (except for aspirin $< \text{or} =$ to 325 mg daily).

Participants were allowed to use approved medications for Alzheimer's disease concomitantly in the Phase 2 and 3 studies.

Baseline demographics were similar between the donanemab and placebo arms in Study AACG.

² Noted in a response dated December 9, 2022, to an information request dated December 7, 2022.

The following table shows baseline demographics for Study AACG.

Table 7. Baseline Demographics for Study AACG

	LY3002813-M (N=131)	Placebo (N=125)	Total (N=256)
Sex			
Female	68 (51.9)	64 (51.2)	132 (51.6)
Male	63 (48.1)	61 (48.8)	124 (48.4)
Age (years)			
Mean (SD)	75.0 (5.6)	75.3 (5.4)	75.1 (5.5)
Median (Min, Max)	75.0 (61, 86)	76.0 (64, 85)	75.5 (61, 86)
Age Group (years)			
<65 years	5 (3.8)	5 (4.0)	10 (3.9)
>=65 and <75 years	55 (42.0)	46 (36.8)	101 (39.5)
>=75 and <85 years	66 (50.4)	71 (56.8)	137 (53.5)
>=85 years	5 (3.8)	3 (2.4)	8 (3.1)
Race			
AMERICAN INDIAN OR ALASKA NATIVE	2 (1.5)	0	2 (0.8)
ASIAN	1 (0.8)	2 (1.6)	3 (1.2)
BLACK OR AFRICAN AMERICAN	5 (3.8)	3 (2.4)	8 (3.1)
MULTIPLE	1 (0.8)	0	1 (0.4)
WHITE	122 (93.1)	120 (96.0)	257 (94.5)
Ethnicity			
HISPANIC OR LATINO	5 (3.8)	3 (2.4)	8 (3.1)
NOT HISPANIC OR LATINO	126 (96.2)	122 (97.6)	248 (96.9)
Country			
CAN	10 (7.6)	11 (8.8)	21 (8.2)
USA	121 (92.4)	114 (91.2)	235 (91.8)
BMI (kg/m2)			
Mean (SD)	26.5 (5.2)	26.3 (4.5)	26.4 (4.9)
Median (Min, Max)	25.8 (15.9, 44.2)	26.1 (17.6, 38.5)	26 (15.9, 44.2)
ApoE ε4 Carrier Status			
Heterozygous Carrier	70 (53.4)	64 (51.2)	134 (52.3)
Homozygous Carrier	25 (19.1)	28 (22.4)	53 (20.7)
Non-Carrier	36 (27.5)	32 (25.6)	68 (26.6)
Unknown	0	1 (0.8)	1 (0.4)
Disease Severity Status			
Mild Cognitive Impairment	25 (19.1)	21 (16.8)	46 (18)
Mild AD	91 (69.5)	93 (74.4)	184 (71.9)
Moderate AD	10 (7.6)	6 (4.8)	16 (6.3)
No baseline or screening MMSE	5 (3.8)	5 (4.0)	10 (3.9)

For labeling purposes, 76% (99/131) of donanemab-treated participants were age 65 to 79 years, and 21% (27/131) were age 80 years and older.

Participants in the donanemab and placebo arms in Study AACG also had similar baseline measures of cognitive function, symptom duration, diagnosis duration, years of education, and use of acetylcholinesterase inhibitors or memantine at baseline.

According to the Alzheimer's Association 2022 Alzheimer's Disease and Facts and Figures, which contains U.S. data related to Alzheimer's disease, approximately two-thirds of Americans with Alzheimer's are women.³ In a population aged 65 years and older with Alzheimer's disease, 27% were between the ages of 65 to 74 years, 37% between 75 to 84 years, and 36% over 85 years. In the same report, studies on race and ethnicity in older populations demonstrate that compared to Whites, African Americans are twice as likely to have Alzheimer's dementia, and Hispanics are about 1.5 times as likely. Between 56 to 65% of people diagnosed with Alzheimer's disease have at least one copy of the ApoE ε4 gene.

A lower frequency of females was observed in the safety population of Study AACG compared to the frequency of females with Alzheimer's disease noted in the Alzheimer's Association 2022 report. The age range of 85 years and over was underrepresented in Study AACG compared to the frequency expected in the population as noted in the Alzheimer's Association 2022 report, likely because participants over the age of 85 years were excluded as per protocol. Blacks and Hispanics or Latinos were underrepresented in Study AACG compared to populations noted in the Alzheimer's Association 2022 report.

This reviewer did not note any significant differences in the baseline demographic characteristics by age, sex, or race in Study AACI Safety Addendum or AACN Dona-Cohort compared to Study AACG. Study AACI Safety Addendum had a higher percentage Latino ethnicity compared to Study AACG (10% versus 3%, respectively), higher frequency of participants with mild cognitive impairment at baseline (33% versus 18%, respectively), lower frequency of acetylcholinesterase inhibitors use at baseline (33% versus 59%, respectively), and lower mean baseline amyloid centiloids compared to Study AACG (82.6 versus 104.4, respectively). Study AACN Dona-Cohort had a higher frequency of participants with mild cognitive impairment compared to Study AACG (34% versus 18%, respectively).

Baseline characteristics for the donanemab-BACE-I arm were similar to Study AACG overall, except for a higher frequency of participants with moderate Alzheimer's disease at baseline (27% versus 6%, respectively) and a lower frequency of memantine use at baseline (7% versus 23%, respectively).

³ Alzheimer's Association. 2022 Alzheimer's disease facts and figures. *Alzheimers Dement* 2022; 18: 700-789. doi: 10.1002/alz.12638

Reviewer comment:

The safety profile of donanemab in patients with more advanced stages of Alzheimer's dementia is unknown as patients enrolled in the key studies for safety were identified as having MCI or mild AD. Given that patients with moderate and severe dementia were not included in the studies, the safety outcomes from these studies potentially underestimate the impact of adverse events in patients with moderate or severe dementia given the increased likelihood of occurrence of other comorbid conditions with advanced dementia, including impaired memory, executive function decline, problems of gait and movement, malnutrition, neuropsychiatric symptoms, and falls.⁴

This reviewer notes that patients who continue treatment with donanemab after achieving amyloid plaque reduction criteria may develop more advanced stages of Alzheimer's disease, and safety outcomes in this population are unknown. In Study AACG, at Week 24 or Week 52 participants who met amyloid plaque reduction criteria had a dose reduction to donanemab 700 mg or to placebo based on the level of amyloid plaque reduction. In Studies AACH Part B, AACI Safety Addendum, and AACN-Dona Cohort, participants who met amyloid plaque reduction criteria were switched to placebo during the study (Week 36 in AACH Part B, Weeks 24 and 52 in AACI Safety Addendum, and Weeks 24 and 52 in AACN-Dona Cohort).

8.2.3. Adequacy of the safety database:

⁴ Feldman H and Woodward M. The staging and assessment of moderate to severe Alzheimer's disease. AAN 2005; 65 (6 suppl 3). DOI: https://doi.org/10.1212/WNL.65.6_suppl_3.S10

Overall, the low number of participants exposed to donanemab for 12 months or more at the proposed dose is low (n=49 at the time of the 90-Day Safety Update), and safety outcomes for this group are less certain than for participants with shorter durations of exposure. The sponsor and this reviewer used different methods to calculate exposure in the safety database. The sponsor's method of calculating exposure, based on a treatment policy approach, included participants who had dose reductions to 700 mg or were switched to placebo. Based on this approach, the sponsor calculated 877 participants with 6-months of exposure and 100 participants with 12-months of exposure in Studies AACG, AACH Part B, AACI Safety Addendum, and AACN Dona Cohort. This reviewer based exposure calculations on participants exposed to donanemab at the proposed dose of 700 mg every four weeks for the first three doses, followed by 1400 mg every four weeks. With this approach, this reviewer calculated 827 participants with 6-months of exposure and 49 participants with 12-months of exposure in Studies AACG, AACH Part B, AACI Safety Addendum, AACN Dona Cohort and AACD (including 7 participants from Study AACD exposed to doses at 20 mg/kg). The reviewer found this approach to be more appropriate as it includes participants exposed to donanemab at the proposed dose in labeling. According to the method of exposure calculation used by this reviewer, although the safety database meets ICH guidelines of at least 300 patients exposed for 6 months, it does not meet ICH guidelines of at least 100 patients exposed for one year. Overall, this reviewer found the number of participants exposed to donanemab for 12 months or more at the proposed dose to be low and the safety database as insufficient to adequately characterize the long-term safety of donanemab in the treatment of Alzheimer's disease.

The population studied was younger than U.S. populations with Alzheimer's disease and minority groups, including Blacks and Hispanics or Latinos, were underrepresented. The safety database consisted primarily of patients with mild cognitive impairment and mild Alzheimer's disease, which is the proposed target population.

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

The reviewer notes differences in the number of AEs in the IDB dataset compared to individual study datasets. Reasons for the difference included different AE analysis methods and different data lock points (leading to a difference of 43 AEs between the individual Study AACG ADAE dataset and the IDB dataset) and inclusion participants from Part A of Study AACH in the individual study ADAE database and not in the IDB database (6 participants causing a difference of 15 AEs). In addition, a difference in the definition of treatment emergent events resulted in a small difference in the number of treatment emergent AEs in the individual study dataset and the IDB (difference of two AEs).

SDTM to ADAM traceability and individual study to ISS assessments were performed by the Office of Computational Science. For Study AACG, the adverse event dataset was not checked

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for individual study ADAM to ISS ADAM traceability due to the individual study ADAM sequence number variable being changed in the ISS ADAE.

In an information response dated August 5, 2022, to an information request dated August 2, 2022, the sponsor notes different data lock points account for 43 more AEs in the IDB ADAE dataset (data lock point October 2021, 1609 AEs) compared to the individual Study AACG dataset (data lock point January 2021, 1566 AEs). At the earlier lock point date, the 43 events occurred in the follow-up period of Study AACG and were not included in analyses of AEs at the individual Study AACG level.

In the same information request, the sponsor notes that the AACH ADAE dataset has 15 more AEs compared to the IDB ADAE dataset, because these AEs occurred in participants in Part A who did not go on into Part B of the study. The sponsor notes that the AACH ADAE dataset has one less TEAE compared to the IDB dataset, because different baselines were used to determine TEAEs (IST-MC-AACG- (b) (6) gingivitis). The IDB AE analysis used the feeder study, Study AACG, as baseline, whereas Study AACH AE analyses used Study AACH as baseline.

In the same information request, the sponsor notes that ADAE dataset from Study AACI had one less treatment event compared to the IDB ADAE dataset ((b) (6) urinary tract infection). This was due to a difference in AE assessments to determine if they were treatment emergent. In Study AACI, an event that ended after informed consent was considered a preexisting condition. In the IDB, an event that ended after informed consent was not considered a preexisting medical condition. In this case, the participant had a urinary tract infection that ended after the date of informed consent and caused the difference in the number of TEAEs between the individual dataset and the IDB.

Overall, the submission was organized. Manuals of Operation for the key studies for the safety review were not included in the submission and were later provided by the sponsor in a response dated July 18, 2022, to an information request dated July 15, 2022.

8.3.2. Categorization of Adverse Events

This reviewer notes that the method of recording AEs of ARIA-H in the adverse event datasets will likely underrepresent the frequency of ARIA-H experienced by participants in Studies AACG, AACH, and AACI. Data from MRIs may provide a better approximation of the frequency of ARIA-H. This reviewer considered the definitions for TEAEs and SAEs to be acceptable. In Study AACG, severity of AEs was based on the judgement of the principal investigator rather than on defined categories and could potentially result in inconsistent AE severity categorization among different principal investigators. *Translation of verbatim terms for adverse events to MedDRA preferred terms was adequate, except as noted below for events related to ARIA-H.*

The protocol for Study AACG specified that all adverse events occurring after signing of the

informed consent form were to be recorded in the case report form. Adverse events were collected at every visit, which occurred every four weeks during the treatment period and during visits in a 52-week follow-up period. The protocol specified that for adverse events that were serious, otherwise medically important, considered related to the investigational product or the study, or that caused the participant to discontinue the investigational product, the participant should be followed until the event resolves, stabilizes, or is reasonably explained. Treatment-emergent adverse events (TEAEs) were defined as events that first occurred or worsened after the randomization date (Visit 2, date of first infusion). Investigators recorded their assessment of the potential relatedness of each adverse event in the case report forms/electronic data entry. A serious adverse event (SAE) was defined as any AE that result in death, initial or prolonged inpatient hospitalization, a life-threatening experience, persistent or significant disability/incapacity, congenital anomaly/birth defect, or an important medical event that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the outcomes listed above. In a response dated August 4, 2022, to an information request dated July 29, 2022, the sponsor noted that adverse events were coded to Medical Dictionary for Regulatory Activities (MedDRA) version 23.1, and then upcoded to version 24.1 for analyses for the integrated database.

The open-label studies provided accurate definitions of AEs and SAEs in their protocols. AEs were collected regardless of relatedness. Open-ended, non-leading verbal questions were used to detect adverse events. AEs were collected at each visit during treatment periods and during follow up periods that were at least five-times the half-life of the drug. Adverse events were assessed by events per participant. Adverse events were coded to Medical Dictionary for Regulatory Activities (MedDRA) version 24.1.⁵

This reviewer noted that for USUBJID I5T-MC-AACG-(b) (6), the verbatim term of “asymptomatic severe ARIA-E with 2 microhemorrhages” was coded to the dictionary derived term “amyloid related imaging abnormality-edema/effusion” but not to “amyloid related imaging abnormality-microhemorrhages and hemosiderin deposits.” In a response dated July 1, 2022, to an information request dated June 29, 2022, the sponsor noted that the protocols for Studies AACG, AACH, and AACI did not have dedicated case report forms to collect ARIA-H symptoms and that symptomatic ARIA-H was a notable event when serious or listed as a reason for discontinuation. The sponsor noted that the protocol in AACG did not require that ARIA-H be reported as an adverse event, and instead, it was captured as an MRI finding. The sponsor noted that MRI data is the more comprehensive and definitive source for identification of ARIA-H.

⁵ Noted by the sponsor in a response dated August 4, 2022, to an information request dated July 29, 2022.

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Reviewer comment: The method of collection of AEs of ARIA-H likely results in under recording of the frequency of ARIA-H events experienced by participants in Studies AACG, AACH, and AACI. Analyses of findings from MRI, as was done in the present review, may better represent the frequency of ARIA-H experienced by participants.

This reviewer noted that two dictionary derived terms were incorrectly coded from the verbatim terms for I5T-MC-AACG- (b) (6) Adverse events with verbatim “left occipital microhemorrhage” and “left frontal microhemorrhage” were coded to the AEDECOD term of “cerebellar microhemorrhage” and should have been coded to the AEDECOD term “cerebral microhemorrhage.”

Also of note, clinical symptoms associated with ARIA-E and infusion site reactions were recorded in a separate dataset from the adverse event dataset.⁶

The reviewer found this method of recording to be acceptable, as it allows for the adverse event dataset to be representative of clinical diagnoses rather than symptoms associated with clinical diagnoses.

8.3.3. Routine Clinical Tests

⁶ Noted in the sponsor’s response dated September 19, 2022, to an information request dated September 14, 2022.

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Overall, this reviewer found the safety assessment methods and timepoints to be adequate for the safety review. Based on timing of assessments in the studies, analyses of vital signs, laboratory values, and ECGs come from Studies AACG, AACH Part B, and AACI Safety Addendum, as AACN had not collected these data at the time of the submission. MRI-related analyses come from Studies AACG, AACH Part B, AACI Safety Addendum, and AACN Dona Cohort.

The following information related to routine clinical tests was collected from the protocols of the Phase 2 and 3 studies.

In Study AACG, systolic and diastolic blood pressure, pulse, and body temperature were measured at baseline, and every four weeks during the treatment period starting at Week 0 through the Early Discontinuation visit, and at Week 88 through 124. Orthostatic blood pressure and pulse was measured after 5 minutes in the supine position and after 3 minutes of standing at Weeks 0, 12, 24, 36, 52, 64, 76, or Early Discontinuation visit, and at unscheduled visits. Weights were measured at baseline, Weeks 0, 12, 24, 36, 52, 64, 76, and the Early Discontinuation visit.

In Study AACG, laboratory tests, including chemistry, hematology, and urine analyses, were collected prior to the administration of intravenous study medication. Chemistry and hematology tests were collected at baseline, Weeks 0, 4, 8, 12, 24, 36, 52, 64, 76, the Early Discontinuation visit, and Weeks 88 through 124. Urine analyses were collected at baseline, Weeks 0, 52, 64, 76, and the Early Discontinuation visit. Hematology, chemistry, and urine analysis labs were assayed at Lilly-designated laboratories.

In Study AACG, ECGs were collected in triplicates and performed prior to the administration of intravenous study medication. ECGs were collected at baseline, Weeks 0, 4, 8, 12, 24, 36, 52, 64, 76, and the Early Discontinuation visit. ECGs were initially interpreted by a qualified physician at the site. All digital ECGs were electronically submitted to a designated central ECG laboratory and a cardiologist conducted an overread on one of the replicates.

In Study AACH Part B, vital signs, including blood pressure, pulse, and temperature were measured at baseline and at all visits during treatment periods and during follow up periods. Orthostatic blood pressure and pulse were measured every 12 weeks starting at Week 0 through the Early Discontinuation visit. Laboratory tests included hematology and clinical chemistry tests were collected at baseline, Weeks 0, 4, 8, 12, 24, 36, 48, 60, and the Early Discontinuation visit. ECGs were measured at baseline and every 12 weeks starting at Week 0 through the Early Discontinuation visit.

In Study AACI Safety Addendum, vital signs, including blood pressure, pulse, and temperature,

were measured at baseline and at all visits during treatment periods and during follow up periods. Orthostatic blood pressure and pulse were measured at Weeks 0, 12, 24, 36, 52, 64, 76, 78, 90, 102, 114, the Early Discontinuation visit, and unscheduled visits. Laboratory tests included hematology and clinical chemistry tests were collected at baseline, Weeks 0, 4, 8, 12, 24, 36, 52, 64, 76, 90, 102, 130, 154, and the Early Discontinuation visit. Urine analyses were measured at Weeks 0, 24, 76, and the Early Discontinuation visit. ECGs were measured at baseline, Weeks 0, 24, 52, 76, and the Early Discontinuation visit.

In Study AACN Dona Cohort, vital signs were measured prior to and within 30 minutes after infusion for clinical management, and not recorded in the case report form. In a response dated June 22, 2022, to information requests dated June 21, 2022, and June 22, 2022, the sponsor noted that ADVS and ADLB datasets were not submitted because vital signs had not been collected and because no participants had reached the timepoint of post-baseline laboratory testing (Week 24). A single, locally-read ECG was performed at screening.

For the schedule for MRIs for assessments related to ARIA, the reader is referred to Section 8.5.1 ARIA of this review.

8.4. Safety Results

8.4.1. Deaths

In the placebo-controlled study, a similar frequency of AEs with fatal outcome was observed between the donanemab and placebo arms (0.8% versus 1.6%, respectively). The frequency of AEs with fatal outcome in the all-donanemab pool did not exceed the frequency of AEs observed in the donanemab arm of the placebo-controlled trial. In a review of narratives submitted by the sponsor from Studies AACG, AACH Part B, AACI Safety Addendum, and AACN-Dona Cohort, this reviewer did not identify any deaths attributable to donanemab exposure. Twenty-two cases of AEs with fatal outcome were reported in the blinded main study of AACI at the time of the 90-Day Safety Update and one additional death from the blinded main study of AACI was subsequently reported after the 90-Day Safety Update. Three of the 23 blinded cases reported ARIA with fatal outcome. Although a role for donanemab could not be established in any of the 23 cases as the data were still blinded at the time of the submission, the three cases associated with ARIA and with fatal outcome are presumed to be related to donanemab for this safety assessment given the severity of ARIA and association of ARIA with amyloid-targeting monoclonal antibodies. Prescribing information will include the observation of fatal cases of ARIA. The contribution of donanemab and of ARIA to these deaths will be further explored when the ongoing trials are submitted.

In Study AACG, a total of two AEs with fatal outcome occurred in the donanemab arm and two in the placebo arm. The frequency of deaths by treatment policy was not higher in the donanemab arm compared to placebo with one death in the donanemab arm and two on

placebo (0.8% versus 1.6%, respectively). The fourth death occurred in the follow-up period. Preferred terms with fatal outcome in donanemab-treated participants were death and pneumonia. Preferred terms in placebo-treated participants were aspiration pneumonia and cardiac arrest.

In the all-donanemab pool, the frequency of adverse events with fatal outcome, based on four events, was 0.3% (4/1293). The two additional AEs with fatal outcome had preferred terms of gunshot wound and acute respiratory failure.

An additional 19 deaths were reported in the safety population of the blinded main study of AACI at the time of the original submission, prior to the 90-Day Safety Update. Preferred terms were death (n=2), pneumonia (n=2), pulmonary embolism (n=2), Alzheimer's dementia, ARIA-E, ARIA-H, community acquired pneumonia, Covid-19 pneumonia, Covid-19, dehydration, myocardial infarction, respiratory failure, respiratory fume inhalation disorder, retroperitoneal hemorrhage, subarachnoid hemorrhage, and suicide attempt.

In Study AACD, there were no deaths in donanemab-treated participants. One placebo-treated participant experienced an SAE with fatal outcome (myocardial infarction).

There were no deaths in Study AACC or participants treated with donanemab and a BACE-I in Study AACG.

A fatality due to ARIA-H in a donanemab-treated participant was noted in the abstract of a publication by Withington and Turner;⁷ however, correspondence between the sponsor and the author of the manuscript indicated that this was in error as the author could neither confirm the identity of the participant nor the treatment arm the participant had been randomized to.⁸

Death Narratives in the All-Donanemab Pool

In the all-donanemab pool, this reviewer notes that a role for donanemab cannot be ruled out in two of the four adverse events with fatal outcome and summarizes the cases here.

Pneumonia, IST-MC-AACG- (b) (6)

85-year-old female with history of moderate AD, transient ischemic attack, coronary artery bypass surgery, hypertension, kidney disease, and reflux, who was hospitalized on Study Day 35 for pneumonia, possibly secondary to aspiration. On the same day, she experienced hypoxia and vomiting. She had received two doses of donanemab, with the most recent dose occurring four days before hospitalization. She was treated with intravenous antibiotics, developed a

⁷ Withington C and Turner R. Amyloid-related imaging abnormalities with anti-amyloid antibodies for the treatment of dementia due to Alzheimer's disease. *Front Neurol* 2022; 13: 1-7. doi: 10.3389/fneur.2022.862369

⁸ Noted in a response dated August 19, 2022, to an information request dated August 17, 2022.

fever, and her respiratory status worsened overnight. The following day, she was less responsive, was moved to hospice, and died.

Reviewer comment: A role for donanemab cannot be ruled out given onset of pneumonia within most recent dose of donanemab. Confounders include risk factors for the development of pneumonia, including her age and history of AD. Increasing age has been shown to be a risk factor for hospitalization for community acquired pneumonia.⁹ Among patients with AD, pneumonia is among the most common causes for hospitalization.¹⁰

Mental status change and Acute respiratory failure, I5T-MC-AACI- (b) (6)

75-year-old female with history of chronic obstructive pulmonary disease, atrial fibrillation, hyperlipidemia, hypertension, and AD was admitted to the hospital with the SAEs of mental status changes and acute respiratory failure on Study Day 38. Her most recent dose had been six days before. A CT of the head showed no abnormalities. The primary care for mental status changes was reported as hypoxia, which resolved the following day. The cause for acute respiratory failure was reported to be caused by multifocal pneumonia due to a bacterial infection and not caused by Covid-19. The same day, the patient became hypotensive, then asystolic, and died due to acute respiratory failure. No autopsy was performed.

Reviewer comment: A role for donanemab in the SAE of acute respiratory failure could not be established as risk factors for the development of acute respiratory failure exist in the case, including multifocal pneumonia secondary to bacterial infection and history of chronic obstructive pulmonary disease. A role for donanemab in the SAE of mental status changes could not be established because of the concurrent event of respiratory failure. A role for donanemab in the event of multifocal pneumonia could not be ruled out as pneumonia was among the most frequently reported SAEs in Study AACG. The reader is referred to the Serious Adverse Events section of this review for the frequency of SAEs of pneumonia.

In the remaining two cases, a role for donanemab could not be established because of delayed onset of the event from the last dose of donanemab (411 days, preferred term of death [cause unknown]¹¹, I5T-MC-AACG- (b) (6)) or secondary to contributory concurrent events (death from gunshot wound inflicted by another person, I5T-MC-AACI- (b) (6)).

⁹ Ramirez J, Wiemken T, Peyrani P, et al. Adults hospitalized with pneumonia in the United States: incidence, epidemiology, and mortality. Clin Infect Dis. 2017; 65(11): 1806-1812. doi: 10.1093/cid/cix647.

¹⁰ James L Rudolph J, Zanin N, Jones R, et al. Hospitalization in community-dwelling persons with Alzheimer's disease: frequency and causes. J Am Geriatr Soc. 2010 Aug;58(8):1542-1548. doi: 10.1111/j.1532-5415.2010.02924.x.

¹¹ Per June 22, 2022, response to an information request dated June 21 and 22, 2022, the sponsor notes that results of autopsy and death certificate were not available.

Deaths in the Blinded Main Study of AACI

At the time of the original submission before the 90-Day Safety Update, two of the events with fatal outcome in blinded main study AACI had preferred terms of ARIA-E and ARIA-H (I5T-MC-AACI- (b) (6) and I5T-MC-AACI- (b) (6)). These cases are summarized here because ARIA is a topic of special interest for this review. Although these cases are still blinded, given the severity of the ARIA and the association of ARIA with amyloid-targeting monoclonal antibodies, cases associated with ARIA are presumed to be related to donanemab for the risk-benefit assessment.

The reader is referred to the [Appendix](#) for a summary of the 17 remaining cases with fatal outcome from the blinded main study of AACI at the time of the original submission before the 90-Day Safety Update. Because the main study of AACI was still blinded at the time of this submission, a role for donanemab in these 17 events with fatal outcome reported at the time of the original submission before the 90-Day Safety Update could not be established. (Of note, another case with preferred term of death that reported symptomatic ARIA-E and symptomatic ARIA-H was reported after the 90-Day Safety Update and is summarized in the 90-Day Safety Update section of the Deaths section of this review (b) (6))

ARIA-E, I5T-MC-AACI- (b) (6)

72-year-old White female ApoE $\epsilon 3/\epsilon 4$ genotype with history of AD, chronic renal failure, open-reduction internal fixation of the knee, situational anxiety who presented to the ER with confusion, agitation, forgetfulness, short attention span, garbled speech, and disorientation, and was diagnosed with the SAE of ARIA-E on Study Day 66. The patient was noted to have declining cognition for several weeks prior to the onset of ARIA-E. In the ER, body temperature was 37.3 Celsius, blood pressure 124/87 (units unspecified), respiratory rate was 16 (units unspecified), heart rate was 88 (units unspecified), and pulse oximetry 97 (units unspecified). The patient was admitted to the hospital and a head CT scan showed severe vasogenic edema. A repeat CT of the head the same day noted in the impression the following: extensive vasogenic edema throughout the right cerebral hemisphere, and probably some within the left occipital lobe remains stable with no discrete enhancing mass. The last dose of study drug (treatment unknown as data is still blinded), her second dose, was 11 days prior to the event.

A CT angiograph without contrast showed a potential subacute right-sided stroke and multifocal areas of vasogenic edema in the right cerebral hemisphere with some confluence and mass effect. A CT angiogram of the head and neck had the following impression: multifocal area of vasogenic edema in the right cerebral hemisphere were nonspecific (full report not available). Concomitant medications included escitalopram oxalate, ginkgo biloba, iron, zinc, vitamin K, vitamin D, coconut oil, and vitamin B12. The patient's treatment for her symptoms included dexamethasone 10 mg, followed by 4 mg twice daily, and levetiracetam 500 mg.

On the third day of hospitalization, an EEG had the following impression: abnormal EEG. This EEG was diffusely and continually abnormal, consistent with the patient's clinical presentation of nonspecific moderately severe encephalopathy. Three days later (Study Day 71), a CT scan of the head had the following impression: New on the unenhanced scan, there was a sliver of hyperdensity within the right posterior and anterior frontal lobe sulci along the vertex suspicious for new foci of subarachnoid hemorrhage; extensive vasogenic edema throughout the right cerebral hemisphere, and probably some within the left occipital lobe remained stable with no discrete enhancing mass. The investigator notes that no MRI reports were received.

Three days later, the patient was discharged to hospice care. Five days later (Study Day 79), she died. The death certificate listed the cause of death as cerebral edema; however, the outcome of ARIA-E was listed as fatal per the study investigator. An autopsy was performed; however, the results were not made available to the site.

The patient's baseline MRI did not show any presence of ARIA-E, > 4 cerebral microhemorrhages, intracerebral hemorrhages, superficial siderosis, severe white matter disease, or MRI findings contraindicating participation in the study. The sponsor assessed the event of fatal ARIA-E as reasonably possibly related to blinded study drug as non-life threatening and non-fatal ARIA-E is an expected event.

Reviewer comment: Although there are no post-screening MRIs in this case, in an email communication dated August 9, 2022, Dr. Ranjit Mani noted that the description of the brain CT is consistent with ARIA-E. This reviewer notes that the participant's death appears to be related to ARIA-E given the findings on the CT of the head.

ARIA-E, ARIA-H, Intracerebral hemorrhage, IST-MC-AACI- (b) (6)

This is a 72-year-old White male, ApoE $\epsilon 3/\epsilon 3$ genotype, with bowel cancer, history of brain trauma, migraines, hypertension, hypercholesterolemia, who was hospitalized for unstable gait and incomprehensible speech aphasia on Study Day 72 and was diagnosed with severe intracerebral hemorrhage and hemorrhagic stroke with mass effect. The patient had taken several acetylsalicylic acid tablets (quantity and dose unknown) at the onset of his speech aphasia. The last dose of study medication (treatment unknown as data is still blinded) had been 44 days before, and he had received 2 doses of study drug. Prior to the event, he had complained of a mild headache on Study Days 46 through 56, and on Study Day 62. On Study Day 62, the study site recommended that he get an MRI sooner than the MRI scheduled for Study Day 71; however, the patient declined, citing an upcoming cataract surgery that contraindicated MRIs be done within 5 days of the surgery. An MRI performed on Study Day 71, one day prior to his symptoms, showed mild ARIA-E, ARIA-H (based on presence of a new microhemorrhage), superficial siderosis in the left frontal lobe (increased from baseline of 50 mm to 65 mm), and superficial siderosis in the right occipital, right parietal, and right temporal non-hippocampal (all measuring < 7 mm). Vital signs in the ER showed a heart rate of 59 (units

unspecified), blood pressure 140/82 (units not specified), respiratory rate of 16 (units not specified), saturation of 97%, glucose 6.2 (units not specified). Physical exam showed right hemineglect, right hemiplegia, regular heart sounds, and low limb exam noted as stroke. He then developed sudden aphasia and right hemiplegia and was seen by neurology and neurosurgery. A CT scan in the ER showed a large left parietal intraparenchymal hemorrhage and vasogenic edema, left frontotemporoparietal intraparenchymal hemorrhage of amyloid appearance with midline shift (5mm), and an adjacent subarachnoid hemorrhage. A repeat CT scan the same day showed a hematoma in the left posterior parietal region, measuring 5.5 x 4.3 cm. A CT angiogram of the carotid arteries showed < 50% stenosis of the left carotid artery and < 30% of the right carotid artery. The platelet count, internationalized normal ratio (INR), activated partial thromboplastin time (PTT), potassium, and creatinine kinase (CK) were normal (platelets $144 \times 10^9/L$ (130-400), INR 1 (reference range not provided), PTT 22.9 sec (20.5-27.5), potassium 5.4 mmol/l (3.5-5.1), and CK 207 u/L (55-170)). Neurosurgery offered surgery for the purpose of decompression; however, his spouse decided upon palliative care and his condition deteriorated later that day. He became comatose, was transferred to palliative care, and died on Study Day 75. The cause of death on the death certificate was hemorrhagic stroke and ARIA-H. His baseline MRI (central read) showed absence of ARIA-E, more than four cerebral microhemorrhages, intracerebral hemorrhages, more than one area of superficial siderosis, severe white matter disease, or other findings contraindicating participation in the study. Superficial siderosis was present in the left frontal region and measured 50 mm. White matter disease was present with beginning of confluence of lesions. Approximately four months before his baseline MRI, the patient had an MRI that showed "hemorrhagic focal area left caudate nucleus (cavernoma?)." Three weeks later a CT angiography showed no arteriovenous malformation.

The investigator assessed the SAE of ARIA-H as related to blinded study drug because ARIA-H was a known adverse event associated with blinded study drug infusion. The sponsor assessed the event of intracerebral hemorrhage as reasonably possibly related to study drug as a brain MRI one day prior to hospitalization showed ARIA-H, which has been identified as an adverse drug reaction for the investigational product.

Reviewer comment: This reviewer notes that the participant's death appears to be related to the intracerebral hemorrhage associated with the findings on the MRI of the brain of ARIA-E and ARIA-H one day prior to his hospitalization. In an email communication dated August 9, 2022, Dr. Mani noted that hemorrhages due to cerebral cavernomas are rarely very large, and the hemorrhage that this patient experienced may be more consistent with an ARIA-related intracerebral hemorrhage. In a review of the screening MRI and Study Day 71 MRI at a meeting dated September 9, 2022, Dr. Ranjit Mani assessed the cavernous malformation noted on the screening MRI as unlikely to have contributed to the bleed, given the difference in areas of the brain that were affected. The ingestion of acetylsalicylic acid prior to the event of ARIA-H may have also contributed to worsening of the outcome of the event.

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90-Day Safety Update

The sponsor notes one additional death in unblinded studies that occurred 6 months after the first dose of study drug and 31 days after the last dose after the cutoff date for the 90-Day Safety Update (5T-MC-AACI- (b) (6)). In this case, a role for donanemab in the event with preferred term of death could not be established due to a lack of information (autopsy not performed, results for request of death certificate still pending).

Taking into consideration the additional death in the all-donanemab pool at the time of the 90-Day Safety Update, the incidence of adverse events with fatal outcome was 0.4% (5/1304). The incidence of death at the time of the 90-Day Safety Update by person-years of exposure to donanemab-M or -C was 0.7% (7 deaths/1,000 person-years [5 deaths/709 person-years]).¹² That does not exceed the reported incidence from Alzheimer's disease in the US of 133.8/1,000 person-years.¹³ This comparison is limited by comparing the population with early-stage Alzheimer's disease (mild cognitive impairment and mild dementia) with the overall Alzheimer's disease population inclusive of later stages.

Three additional deaths were reported in the blinded main study of AACI at the time of the 90-Day Safety Update. Preferred terms included completed suicide (n= 2) and respiratory arrest. A role for donanemab in the AEs with fatal outcome could not be established as treatment was still blinded. In both cases of suicide, the patients had risk factor of depression and had received their first dose of study drug over 9 months before the onset of the event (I5T-MC-AACI- (b) (6) and 5T-MC-AACI- (b) (6)). In the case of respiratory arrest, the patient had concurrent events that were likely contributory including gastric outlet obstruction, pancreatitis, and ureteropelvic junction obstruction (I5T-MC-AACI- (b) (6)).

One additional death was reported prior to completion of this review, and the events of symptomatic ARIA-E and symptomatic ARIA-H were also reported in the case. The case is summarized here.

Death, ARIA-E, and ARIA-H, Participant (b) (6) /Manufacturer Report # US202211015256

This is a 76 year-old White male from blinded main study AACI with a history including chronic kidney disease stage 3, hypertension, hyperlipidemia, type 2 diabetes mellitus, aortic arteriosclerosis, balance disorder, and heterozygous for ApoE ε4 who presented to the ER (on

¹² This reviewer calculated person-years of donanemab-M and donanemab-C exposure at the time of the 90-Day Safety Update based on the number of months of donanemab exposure ([IDB ADEX 90 Day Safety Update dataset, EXDOSE = 700, 1400, 2800 where 1 infusion = 1 month]/12).

¹³ Ganguli M, Dodge H, Shen C, et al. Alzheimer's Disease and Mortality: A 15-Year Epidemiological Study. Arch Neurol 2005; 62(5): 779-784. doi: 10.1001/archneur.62.5.779.

Study Day 427) after developing increased confusion for two weeks, nausea, bowel incontinence, and vomiting, was admitted for symptomatic ARIA-E and ARIA-H, and died 18 days later.¹⁴ Additional symptoms prior to presentation to the ER included worsening balance and headaches for two weeks. The patient had received 10 doses of study drug prior to presentation to the ER, with the most recent dose occurring 24 days before. An unscheduled MRI obtained four days before presentation to the ER (Study Day 423) showed severe ARIA-E (right frontal; left frontal; right temporal, non-hippocampal; right parietal; left parietal; right occipital) and more than 10 new microhemorrhages (43 total microhemorrhages). At baseline, the patient’s MRI showed no ARIA-E, microhemorrhages, superficial siderosis, or intracerebral hemorrhage. Vital signs upon admission to the ER included an elevated blood pressure (213/107 [units not reported]), temperature 36.9 (units not reported), pulse of 75 (units not reported), and respiratory rate of 18 (units not reported). A neurological exam showed left-sided weakness and left-sided neglect. The impression from a CT scan was diffuse vasogenic edema within the right cerebral hemisphere with 2 mm of right to left midline shift. An MRI the following day showed ARIA-E with extent greater than 10 cm and involvement in multiple areas of the brain (right frontal, right temporal, non-hippocampal, right parietal, right occipital, left frontal, left parietal) and greater than 10 microhemorrhages. The patient was started on dexamethasone and ondansetron and discharged to hospice that day. Ten days later, he was discharged to a skilled nursing facility where he passed 9 days later (SAE term: death of unknown cause). No autopsy was performed. He was also reported to die due to symptomatic ARIA-E and symptomatic ARIA-H. Given the conflicting information, the cause of death is to be confirmed. Receipt of the death certificate is still pending.

Additional events experienced by the patient and not included above are outlined in the table below.

Table 8. Additional Events Occurring in Participant (b) (6) in Blinded Main Study AACI.

Study Day	Events
79	The patient was noted have severe ARIA-E on a scheduled MRI (right frontal; right temporal, non-hippocampal; right parietal; right occipital) and more than 10 new microhemorrhages (11 total). The study drug was temporarily discontinued on this day. The patient had had three doses of study drug with the most recent dose occurring 15 days before severe ARIA-E was diagnosed by MRI.
85	The patient developed headache (mild severity), which resolved the same day.
107	An unscheduled MRI showed that the ARIA-E had decreased in size and was still severe. Additionally, the patient had developed more than 10 new

¹⁴ Information for the narrative noted in the sponsor’s submissions to IND 109157 on December 23, 2022, December 28, 2022, January 3, 2023, and January 5, 2023.

Study Day	Events
	microhemorrhages (23 total microhemorrhages).
112	The patient developed balance disorder (mild severity), which resolved the same day.
135	An unscheduled MRI showed moderate ARIA-E and 1 new microhemorrhage (24 total microhemorrhages).
167	An MRI showed mild ARIA-E and no new microhemorrhages.
195	An MRI showed resolution of ARIA-E and no new microhemorrhages.
202	Study drug was resumed (Week 28, Visit 9), at a dose of 700 mg or placebo equivalent.
209	The patient developed intermittent headaches and the study drug was temporarily discontinued
232	An MRI showed no ARIA and the study drug infusions were resumed at a dose of 700 mg or placebo equivalent
331	Starting with 8 th infusion, the dose was adjusted to 1400 mg or placebo equivalent
427	Presentation to ER for current event

Reviewer comment: A role for donanemab in the events of ARIA and death cannot be established as treatment for this participant is still blinded. The event of death is likely related to the events of ARIA given the report that the patient died due to symptomatic ARIA-E and symptomatic ARIA-H. The sponsor is currently awaiting receipt of the death certificate.

8.4.2. Serious Adverse Events

The data sources I used for this summary of SAEs included the narrative summaries and case report forms submitted by the applicant.

SAEs were reported with equal frequency in donanemab and placebo arms in Study AACC (18%). SAEs by preferred term in donanemab-treated participants in Study AACC with highest frequency included pneumonia (4%), ARIA-E, infusion related reaction, pulmonary embolism, and syncope (each 2%). In the all-donanemab pool at the time of the 90-Day Safety Update, ARIA-E, syncope, and pneumonia were the most frequently reported SAEs by preferred term.

There were no SAEs of acute pancreatitis, agranulocytosis, aplastic anemia, bone marrow depression, disseminated intravascular coagulation, hemolytic anemia, liver failure, pancytopenia, Stevens Johnson syndrome, toxic epidermal necrolysis, rhabdomyolysis, sudden death, torsades, thrombotic thrombocytopenia purpura, or ventricular fibrillation.

Adverse events in this review were evaluated by preferred term and by groupings of closely related preferred terms called MedDRA query groups (MQG). The reader is referred to the

Appendix for a list of MQGs in this review and the preferred terms that make up the groupings.

In Study AACG, participants in the donanemab and placebo arms had the same frequency of experiencing at least one SAE (17.6%: 23/131 and 22/125, respectively).

The SAE of pneumonia was reported with higher frequency in the donanemab arm compared to placebo in Study AACG (4% versus 1%, respectively). The following table shows SAEs by preferred term with frequency of at least 2% higher in the donanemab arm compared to placebo in Study AACG.

Table 9. SAEs by Preferred and Grouped Terms with Frequency of at least 2% higher in the Donanemab Arm Compared to Placebo in Study AACG

Adverse Event	DON N=131 n (%)	Placebo N=125 n (%)
Infection MQG	8 (6)	3 (2)
Pneumonia	5 (4)	1 (1)
Bacterial Sepsis	1 (1)	0
Clostridium Difficile Colitis	1 (1)	0
Gastroenteritis	1 (1)	0
Aspiration Pneumonia	0	1 (1)
Staphylococcal Infection	0	1 (1)
Urinary Tract Infection	0	1 (1)
Amyloid Related Imaging Abnormality-edema/Effusion ¹	2 (2)	0
Infusion Related Reaction	2 (2)	0
Pulmonary Embolism	2 (2)	0
Syncope	2 (2)	0

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

MQG: MedDRA Query Group. The reviewer created this using the IDB ADAE dataset submitted in a response by the sponsor on August 5, 2022, to an information request dated August 2, 2022, with SAFFL = Yes, StudyID=AACG, PCIN57FL = Yes, TRTEMFL= yes, AESER = Yes.

At the time of the 90-Day Safety Update, 8% (109/1304) of participants in the all-donanemab pool reported at least one SAE. Infection, ARIA-E, and fracture were the most frequently SAEs reported at the time of the 90-Day Safety Update. ARIE-E, syncope, and pneumonia were the most frequently reported SAEs by preferred term. The following table shows SAEs with frequency of at least 1% by preferred term and groups of preferred term in the all-donanemab pool at the time of the 90-Day Safety Update.

Table 10. SAEs by Preferred Term and Grouped Terms with Frequency of at Least 1% in the All-Donanemab Pool in the 90-Day Safety Update.

Adverse Event	DON N=1304 n (%)
Infection MQG	21 (2)
Pneumonia	8 (1)
Diverticulitis	3 (<0.5%)
Bacterial Arthritis	1 (<0.5)
Bacterial Sepsis	1 (<0.5)
Clostridium Difficile Colitis	1 (<0.5)
Gastroenteritis	1 (<0.5)
Kidney Infection	1 (<0.5)
Peritoneal Abscess	1 (<0.5)
Peritonitis	1 (<0.5)
Aspiration Pneumonia	1 (<0.5)
Salmonellosis	1 (<0.5)
Sepsis	1 (<0.5)
Fracture MQG	10 (1)
Rib Fracture	3 (<0.5)
Hip Fracture	2 (<0.5)
Femoral Neck Fracture	1 (<0.5)
Humerus Fracture	1 (<0.5)
Multiple Fractures	1 (<0.5)
Patella Fracture	1 (<0.5)
Upper Limb Fracture	1 (<0.5)
Wrist Fracture	1 (<0.5)
Allergic Reaction and Hypersensitivity MQG	9 (1)
Infusion Related Reaction	5 (<0.5)
Anaphylactic Reaction	3 (<0.5)
Drug Eruption	1 (<0.5)
Arrhythmia FDA N MQG	9 (1)
Atrial Fibrillation	5 (<0.5)
Atrial Flutter	1 (<0.5)
Bradycardia	1 (<0.5)
Sinus Node Dysfunction	1 (<0.5)
Supraventricular Tachycardia	1 (<0.5)
Syncope	9 (1)

Adverse Event	DON N=1304 n (%)
Amyloid Related Imaging Abnormality-edema/Effusion ¹	8 (1)

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

MQG: MedDRA Query Group. The reviewer created this using the IDB ADAE dataset submitted 8.25.22, TRT01A = inversion of Dona-C, SAFFL = Yes, LYIN57FL = Yes, TRTEMFL = yes, AESER = Yes.

At the time of the 90-Day Safety Update, the sponsor noted that 10% (165/1727) of participants from the blinded main study of AACI reported at least one SAE.¹⁵ The most frequently reported SAEs by preferred term were syncope (1%, 16/1727), amyloid related imaging abnormality-edema/effusion (1%, 12/1727) and Covid-19 (1%, 9/1727).

SAE Narratives

The reviewer reviewed narratives of SAEs that occurred while the patient was on treatment with donanemab or within 57 days of the last dose of donanemab in Phase 1, 2 and 3 Studies in the adverse events dataset that were reported by the time of the 90-Day Safety Update, including participants exposed to BACE-I in Study AACG. Of note, the number of SAEs reported in the tables for Phase 2 and 3 studies in the previous section is higher than the SAEs reported in the SAE Narratives section as frequencies in the previous section were based on SAEs occurring within different treatment periods (in the treatment period plus 57 days, which includes AEs occurring in participants who were receiving donanemab or placebo infusions, versus on treatment plus 57 days, which includes participants who were receiving donanemab). Therefore, the previous section includes SAEs with onset occurring greater than 57 days from the date of last exposure to donanemab.¹⁶

The review of narratives of SAEs related to topics of special interest including ARIA and allergic reaction/hypersensitivity.

The reviewer also reviewed narratives of most frequently reported SAEs in Study AACG, including pneumonia, pulmonary embolism, syncope, and infection.

The reviewer also reviewed SAEs of intracerebral hemorrhage, arrhythmia, falls, dehydration, fracture, seizure, encephalopathy/mental status changes, suicide-related events, diabetic ketoacidosis, acute kidney injury, and acute respiratory failure.

¹⁵ Noted in Table 6.5 of the Safety Update Report, submitted August 17, 2022.

¹⁶ SAEs with onset occurring greater than 57 days from the date of last exposure to donanemab: atrial fibrillation/I5T-MC-AACG-(b) (6), clostridium difficile colitis/I5T-MC-AACG-(b) (6) herpes zoster/I5T-MC-AACI-(b) (6) (b) (6) hip fracture/I5T-MC-AACG-(b) (6) multiple fractures/I5T-MC-AACI-(b) (6) pneumonia/I5T-MC-AACG-(b) (6) pulmonary embolism/I5T-MC-AACG-(b) (6) and syncope/I5T-MC-AACG-(b) (6)

ARIA-E

For the topic of ARIA-E, this reviewer searched Phase 2 and 3 studies for SAEs with preferred terms potentially related to the topic of ARIA-E, including amyloid related imaging abnormality-edema/effusion, brain edema, and vasogenic cerebral edema.

Ten SAEs with preferred term of amyloid related imaging abnormality-edema/effusion were reported in 10 participants in Phase 2 and 3 studies while on treatment with donanemab or within 57 days of treatment.¹⁷ A role for donanemab in the 10 cases with SAEs of ARIA-E is likely given the time between AE onset and dosing of donanemab, and because ARIA has been associated with aducanumab and lecanemab, approved amyloid-directed monoclonal antibody drugs.¹⁸

Seven of the 10 participants were female. Median age was 76 years (range 69 to 82 years). Nine of the 10 SAEs had started by Study Day 75. The majority of SAEs were reported as recovered or resolved. Median time to recovery or resolved status was 67 days (range 10-148 days). Participants had been exposed to between 1 and 5 doses of donanemab. Seven of the 10 participants were homozygous or heterozygous $\epsilon 4$ carriers. Four cases had concurrent ARIA-H at some timepoint during the ARIA-E event. Two cases had concomitant antithrombotic use (acetylsalicylic acid 81 mg daily in both cases). One of the two cases with acetylsalicylic acid use also had a concurrent ARIA-H event. In four of the cases, treatment included steroids (dexamethasone (n=3), methylprednisolone (n=5), prednisone). Seven of the ten cases resulted in hospitalization.

All the cases were symptomatic. Symptoms reported in the narratives included aphasia (n=3), headache (n=3), confusion (n=2), abnormal coordination, alexia without agraphia, altered mental status, arm weakness, asthenia, ataxia, blurred vision, cognitive disorder, decreased appetite, disorientation, disturbance in attention, dizziness, dysphagia, dyslexia, eye movement disorder, fatigue, gait disturbance, Gerstmann syndrome, hemineglect, intellectual disability, lethargy, poor balance, psychomotor retardation, rare-word finding difficulty, slow coordination, visual agnosia, and visual field neglect.

Screening MRI findings were normal in four cases or did not have microhemorrhages or superficial siderosis at screening in one case. In the remaining five cases, four cases reported

¹⁷ Participants with SAEs of ARIA-E: I5T-MC-AACG- (b) (6) I5T-MC-AACG- (b) (6) I5T-MC-AACG- (b) (6) I5T-MC-AACG- (b) (6) I5T-MC-AACI- (b) (6) I5T-MC-AACI- (b) (6) I5T-MC-AACI- (b) (6) I5T-MC-AACI- (b) (6) I5T-MC-AACI- (b) (6) I5T-MC-AACI- (b) (6) and I5T-MC-AACI- (b) (6) In the sponsor's response dated November 1, 2022, to an information request dated October 31, 2022, the sponsor acknowledged that differences existed in the number of serious ARIA events reported in the MRI and AE datasets (8 events of serious ARIA-E versus 10 events of serious ARIA-E, respectively) in part because of differences in timing in when an MRI demonstrated an ARIA event and when an event was noted as serious by the investigator.

¹⁸ Aduhelm. Labeling-Prescribing Information. Drugs@fda.gov. Action date April 29, 2022. Accessed July 15, 2022.

involvement of the left frontal lobe with either microhemorrhages, superficial siderosis, or both at screening. The location of the microhemorrhages was not reported in one case. One case noted the size of the area with superficial siderosis at baseline (13 mm). No cases reported more than two microhemorrhages at screening.

The following table summarizes characteristics of the serious cases of ARIA-E in Phase 2 and 3 Studies.

Table 11. Summary of Narratives of SAEs of ARIA-E in Phase 2 and 3 Studies

Parameter	SAEs of ARIA-E in Phase 2 and 3 Studies (n=10)
Sex	Male (3) Female (7)
Age (years)	Median: 76, Range: 69 - 82
Race	White (10)
E4 carrier status	Homozygous (5) Heterozygous (2) Non-carrier (2) Unknown (1)
Screening MRI findings	Normal (4) Microhemorrhages (2) Superficial siderosis (2) Microhemorrhages and superficial siderosis (1) No microhemorrhage or superficial siderosis (1)
Study Day of Start of SAE	Median: 60, Range: 32 – 131
Time between the first dose and onset of ARIA-E (days) ^a	Median: 58, Range: 22 – 129
Time between the most recent dose and onset of ARIA-E (days) ^a	Median: 19, Range: 0 – 22
Number of donanemab infusions prior to onset of ARIA-E ^a	Median: 3, Range: 1 – 5
AE outcome	Recovered/Resolved (8) Recovering/Resolving (2)
Duration of AEs with Recovered/Resolved status (days)	Median: 67, Range: 10 – 148
Study Drug Disposition	Permanent discontinuation (7) Temporarily held (3)
Concurrent ARIA-H ^b	Yes (4) No (6)

Parameter	SAEs of ARIA-E in Phase 2 and 3 Studies (n=10)
Concomitant Antithrombotic Use	Aspirin 81 mg daily (2) None (8)
Treatment with steroids	(4)
Hospitalization	(7)
Symptoms	Symptoms reported in the narratives included aphasia (n=3), headache (n=3), confusion (n=2), abnormal coordination, alexia without agraphia, altered mental status, arm weakness, asthenia, ataxia, blurred vision, cognitive disorder, decreased appetite, disorientation, disturbance in attention, dizziness, dysphagia, dyslexia, eye movement disorder, fatigue, gait disturbance, Gerstmann syndrome, hemineglect, intellectual disability, lethargy, poor balance, psychomotor retardation, rare-word finding difficulty, slow coordination, visual agnosia, and visual field neglect

^aRegardless of whether the initial ARIA-E event was serious (days)

^bAt any timepoint during ARIA-E event

In Phase 1 studies, one SAE of vasogenic cerebral edema/ARIA-E was identified in one donanemab-treated participant (AACD- (b) (6)).

I summarize one case of ARIA-E/ARIA-H here. The reader is referred to the appendix for narratives on an additional case of ARIA-E/ARIA-H ([I5T-MC-AACG- \(b\) \(6\)](#)) and a case of ARIA-E ([I5T-MC-AACG- \(b\) \(6\)](#)).

ARIA-E, ARIA-H (I5T-MC-AACG- (b) (6))

82-year-old male with PMH of AD and hypercholesterolemia, APOE genotype carrier $\epsilon 4\epsilon 4$, who developed the SAEs of ARIA-E and ARIA-H on Study Day 257, 52 days after receiving the first dose of donanemab. The most recent dose of donanemab was 20 days prior (2nd dose). The screening MRI showed 2 microhemorrhages and cortical superficial siderosis in the left frontal lobe. On Study Day 257, the patient experienced sudden onset of confusion, aphasia, bifrontal and bioccipital headache. He was transported to the hospital and reported other symptoms, including decreased appetite, dysphagia, disorientation, gaze deficit, abnormal coordination, and lethargy. He was hospitalized with symptoms of focal deficits, unilateral weakness, altered mental status and was diagnosed with ARIA-E and ARIA-H. The study drug was withdrawn due to the events of ARIA-E and ARIA-H. On Study Day 258, he had worsened mental status, lethargy, unsteadiness on his feet, inability to name common objects, headache, decreased

response to stimuli, and also had diaphoresis and dyspnea. The central read of an MRI obtained on that day showed severe new ARIA-E (area of FLAIR hyperintensity measuring greater than 10 cm), white matter and/or sulcal involvement with associated gyral swelling and sulcal effacement. ARIA-H was non-evaluable. A CT of the head and neck performed that day showed no acute intracranial processes, aneurysms, vascular occlusions, intracranial stenosis, or significant stenosis in the extracranial vertebral or carotid arteries. On Study Day 259, the patient was awake and reported to be almost back to baseline. He received treatment with mirtazapine, levetiracetam, glucose/sodium chloride, docusate, senna, and paracetamol. On Study Day 263, he was discharged from the hospital. On Study Day 294, his MRI showed moderate plus ARIA-E (5 to 10 cm) in right and left frontal, right temporal, non-hippocampal, left temporal, right and left parietal, right and left occipital lobes; > 10 microhemorrhages in left and right occipital, right parietal, left temporal, and non-hippocampal, and three areas of superficial siderosis in the left and right frontal lobe. By Study Day 312, all his associated symptoms of ARIA-E had resolved. On Study Day 385, the patient's MRI scan was found to have resolved ARIA-E and stabilized ARIA-H. Both AEs were reported as recovered that day.

Reviewer comment: A role for donanemab in the events of ARIA-E and ARIA-H is likely given the time between AE onset and dosing of donanemab, and because ARIA has been associated with aducanumab and lecanemab, approved amyloid-directed monoclonal antibody drugs.

ARIA-H

For the topic of ARIA-H, this reviewer searched Phase 2 and 3 studies for SAEs with preferred terms potentially related to the topic of ARIA-H, including amyloid related imaging abnormality-microhemorrhages and hemosiderin deposits, brain stem microhemorrhage, cerebellar microhemorrhage, cerebral hemosiderin deposit, cerebral microhemorrhage, and superficial siderosis of central nervous system.

Four SAEs with preferred term of amyloid related imaging abnormality-microhemorrhages and hemosiderin deposits were reported in four participants in Phase 2 and 3 studies while on treatment with donanemab or within 57 days of treatment.¹⁹ A role for donanemab in the four SAEs of ARIA-H is likely given the time between AE onset and dosing of donanemab, and because ARIA-H has been associated with aducanumab and lecanemab, approved amyloid-directed monoclonal antibody drugs.²⁰

All of these participants also experienced concurrent AEs of ARIA-E, three of which were SAEs. Two of the four participants were female. Median age was 76 years (range 73 to 82). SAEs of ARIA-H had onset between Study Day 52 and 75. Two were reported as recovered/resolved and

¹⁹ Participants with SAEs of ARIA-H: I5T-MC-AACG- (b) (6) I5T-MC-AACG- (b) (6) I5T-MC-AACI- (b) (6) and I5T-MC-AACI- (b) (6)

²⁰ Aduhelm. Labeling-Prescribing Information. Drugs@fda.gov. Action date April 29, 2022. Accessed July 15, 2022.

two were reported as not recovered/not resolved. Time to recovery was 58 days in one case and 128 days in the second. All four participants were homozygous $\epsilon 4$ carriers. One of the four cases reported concomitant antithrombotic use (aspirin 81 mg daily). Screening MRIs in two cases showed two microhemorrhages (one of the cases also with lacunar infarct), and in the remaining two cases, superficial siderosis in the left frontal lobe.

Intracerebral hemorrhage

The reviewer searched for the following terms related to intracerebral hemorrhage: cerebral hematoma and cerebral hemorrhage.

One SAE of intracerebral hemorrhage was reported in one donanemab-treated participant in Phase 2 and 3 studies in addition to blinded Subject [IST-MC-AACI- \(b\) \(6\)](#) described in the Deaths section of this review, and two events of intracerebral hemorrhage that were considered nonserious ([IST-MC-AACI- \(b\) \(6\)](#) and [IST-MC-AACI- \(b\) \(6\)](#)), described in the ARIA section of this review. A role for donanemab in the SAE of intracerebral hemorrhage described below (AACI- (b) (6)) cannot be excluded given proximity of occurrence of intracerebral hemorrhage with an ARIA-E event, although the patient had other contributory factors. This reviewer summarizes the case here.

Intracerebral hemorrhage, AACI- (b) (6)

This is a 79-year-old male with past medical history of hypertension, coronary artery disease, bradycardia, atrial fibrillation, and hyperlipidemia, ApoE genotype carrier ($\epsilon 3\epsilon 4$), history of tobacco use who developed the SAE of intracerebral hemorrhage on Study Day 74, which occurred 17 days after the third dose of donanemab and 43 days after the development of ARIA-E. Concomitant medications included apixaban, dofetilide, and lovastatin. On Study Day 31, the patient experienced the AE of ARIA-E (moderate severity) and confusional state (mild severity), which started on the same day as the second dose of donanemab. An MRI on Study Day 67 showed moderate ARIA-E in the left and right cerebellum, left and right parietal lobes, and right frontal lobe, and a lacunar infarct in the right cerebellum (5 mm). On Study Day 74, the caregiver reported that the patient lost his balance and fell on the sidewalk while running, and developed bleeding to the back of the brain, hemorrhagic stroke, worsening vision, and confusion. The patient was hospitalized on the same day for the SAE of intracerebral hemorrhage (severe severity) and underwent CT without contrast and was diagnosed with a right occipital lobe intraparenchymal hemorrhage with rupture into the right lateral ventricle and mild ventriculomegaly. An MRI performed on that day showed no change in appearance to the hemorrhage in right occipital lobe, slightly more blood evident in occipital horn of left lateral ventricle, and possible small amount along posterior cerebral hemisphere. The patient's partial thromboplastin time was 48.8 sec (reference range: 25.1-36.5 sec). On Study Day 76, the patient's prothrombin time was 13.3 sec (reference range: 10-12.8 sec) and international normal ratio was 1.14 (reference range: 0.8-1.1). On Study Day 77, the patient underwent MRI

scan which showed right occipital lobe parenchymal hemorrhage with intraventricular extension and surrounding vasogenic edema. On Study Day 80, the patient was transferred to a rehabilitation center. His condition was noted to be improved the following day and had vision problems in only the left eye. On Study Day 88, the patient was reported to be experiencing sundowning, hallucinations, and restlessness at night. He was started on quetiapine. The patient's agitation, memory issue, and vision in the left eye remained unchanged. On Study Day 144, he was discharged was reported as still recovering from the event. A follow-up MRI Study Day 130 showed mild+ severity of ARIA-E with increased size in the left and right cerebellum, left and right parietal lobes, right occipital lobe, and right frontal lobe, and an intracerebral hemorrhage of 29 mm in right occipital lobe. The study drug was temporarily interrupted due to the SAE of intracerebral hemorrhage. As of the 90-Day Safety Update, the last dose of study drug was administered on Study Day 58. The symptom of confusion associated with ARIA-E was ongoing at the time of data cut-off. The SAE of intracerebral hemorrhage was resolving at the data cut-off.

Reviewer comment: A role for donanemab in the AE of ARIA-E is likely given temporal association with donanemab and AE onset. A role for donanemab in the SAE of intracerebral hemorrhage cannot be ruled out given proximity of occurrence of intracerebral hemorrhage with ARIA-E. Contributory factors for the event of intracerebral hemorrhage also included the preceding event of fall and concomitant medication use with apixaban.

Other SAEs Related to CNS Hemorrhage

The reviewer searched for the following terms related to CNS hemorrhage: central nervous system hemorrhage, hemorrhagic stroke, intraventricular hemorrhage, intracranial hemorrhage, subarachnoid hemorrhage, subdural hematoma, and subdural hemorrhage.

One SAE of subarachnoid hemorrhage was reported in one donanemab-BACE-I treated participant in Study AACG (I5T-MC-AACG- (b) (6)). In this case, a role for donanemab could not be ruled out, and the case is summarized here.

Subarachnoid hemorrhage (I5T-MC-AACG- (b) (6))

84-year-old female with history of AD, depression, food allergies, hyperlipidemia, headache, hypothyroidism, APOE genotype e3e3 also with treatment-emergent anti-drug antibodies (titer >20,480) who developed the SAE of subarachnoid hemorrhage on Study Day 199, on the same day as the fifth dose of donanemab (700 mg q 4 weeks IV). As per protocol, the patient received oral BACE inhibitor every day in addition to monthly donanemab infusions.

On Study Day 56, and on the same day as the third dose of donanemab (700 mg q 4 weeks IV), the patient was diagnosed with infusion-related reactions (AEs of flushing of skin during infusion, post-infusion headache, and chills, each mild in severity). Anti-drug antibody titer level

was 1:1280 on that day. The patient recovered from the AEs on the same day. On the same day, the patient was discontinued from the oral daily BACE inhibitor, based on a decision by the sponsor under amendment (d) of the protocol for Study AACG.²¹

On Study Day 78, an MRI scan showed ARIA-E that was moderate in severity. The patient's baseline MRI scan showed 2 microhemorrhages. The event occurred 22 days after the third dose. This was reported as recovered/resolved on Study Day 162.

On Study Day 171, the patient resumed treatment with donanemab (fourth dose, 700 mg q 4 weeks IV).

On the day of the fifth dose of donanemab (Study Day 199), the patient developed the SAE of subarachnoid hemorrhage. The following table shows vital signs and symptoms reported by the patient on the day of the infusion (700 mg q 4 weeks IV).

Table 12. Vital Signs and Symptoms on Study Day 199 for I5T-MC-AACG- (b) (6)

Time	Event
Pre-infusion	BP: 115/58 mmHg, HR 67 bpm, temperature: 36.5 degrees C.
10:26 am	Blinded IV study drug was started
10:29 am	Patient complained of flushing and feeling hot
10:30 am	Patient complained of shortness of breath and the infusion was paused
10:33 am	BP: 181/103 mmHg, HR: 61 bpm, oxygen saturation reading on room air: 92%
10:35 am	Patient developed throbbing occipital headache
10:37 am	BP: 121/59 mmHg, HR 57 bpm, oxygen saturation on room air: 96%
10:42 am	HR: 59 bpm, oxygen saturation on room air: 94% The patient reported that the flushing and shortness of breath had subsided
10:49 am	BP: 100/54 mmHg, HR: 61 bpm, temperature: 36.6 degrees C, oxygen saturation on room air: 98%. The primary investigator decided to stop infusion due to the observed reaction. The total dose administered was 19.63 mL. The headache was reported to have subsided.
11:12 am	Upon drawing of the infusion reaction bloodwork, the patient complained of a sudden severe headache and difficulty breathing. The patient became short of breath, stridulous, and complained of chills.
11:33 am	The patient was transferred via ambulance to the hospital. The patient still complained of headache; however, the shortness of breath had resolved.

BP: blood pressure, HR: heart rate

²¹ Discontinuation date of BACE-I for this participant is noted in the CSR for Study AACG, page 46.

A CT angiogram showed subarachnoid hemorrhage and no aneurysm or vascular abnormality (further details not available).²² A neurologic exam upon hospital admission did not show any deficits. An electrocardiogram showed normal sinus rhythm. Neurosurgical intervention was deemed not necessary. Concomitant medications included preservative multivitamins, betamethasone dipropionate, diclofenac, donepezil, ergocalciferol, escitalopram, fenofibrate, lansoprazole, levothyroxine, memantine, mupirocin, olanzapine, and vitamin B12. A review of the participant's platelet counts before and after the onset of the event of subarachnoid hemorrhage (Study Days 171 and 207) indicated that the counts were within the normal reference range ($273 \times 10^9/L$ and $183 \times 10^9/L$, respectively [normal range $130-394 \times 10^9/L$]).

The following day (Study Day 200), the CT showed stable subarachnoid hemorrhage and the patient was discharged. The patient had no history of tobacco use. On Study Day 206, the anti-drug antibody level had increased to a maximum of 1:327680. The patient was considered recovering from the SAE of subarachnoid hemorrhage and permanently discontinued from the study drug and from the study because of the SAE.

*Reviewer comment: A role for donanemab in the event of subarachnoid hemorrhage cannot be ruled out given that the event occurred during a donanemab infusion. Of note, the onset of headache was preceded by elevated blood pressure (181/103 mmHg), which is a likely contributory factor to the SAE of subarachnoid hemorrhage. Although the AE of infusion related reaction was not reported on the day of the subarachnoid hemorrhage, the patient experienced elevated blood pressure, flushing, feeling hot, and shortness of breath, which are symptoms consistent with an infusion related reaction. A role for donanemab in the symptom of infusion reaction is likely given onset during the donanemab infusion. A role for the infusion related reaction in the SAE of subarachnoid hemorrhage is likely, given that the patient experienced elevated blood pressure prior to the onset of headache.*²³

Seizure

Two SAEs of seizure were reported in two participants in Phase 2 and 3 studies while on treatment with donanemab or within 57 days of treatment. A role for donanemab in one case of seizure was unlikely as the seizure occurred in the setting of metabolic encephalopathy and Covid-19 infection (I5T-MC-AACI-(b) (6)). A role for donanemab in the SAE of metabolic encephalopathy could not be established because of the concurrent event of Covid-19 infection. In the second case, a role for donanemab could not be established because of

²² Further details of report of CT angiogram not available as per the sponsor's response dated September 7, 2022, to an information request dated September 6, 2022.

²³ Chung, C. Managing premedications and the risk for reactions to infusional monoclonal antibody therapy. The Oncologist 2008; 13(6): 725-732. DOI: 10.1634/theoncologist.2008-0012; PMID: 18586928

concurrent events of subarachnoid bleed and subdural hygromas. The case is summarized here.

SAEs of Seizure and Subdural Hematoma, subarachnoid bleed, I5T-MC-AACI- (b) (6)

A 68-year-old female with medical history of sleep apnea, headache, APOE genotype ε3ε4 who developed the SAE of seizure 75 days after the first dose of donanemab and 19 days after the 3rd dose of donanemab (Study Day 57). MRI findings from Study Day 26 showed no microhemorrhages and white matter abnormalities. On Study Day 67, the patient developed worsening headache. On Study Day 69, the patient fell three times while getting off a chairlift while skiing and hit her head in the snow. On Study Day 71, an MRI showed a subarachnoid bleed in the right frontal lobe, new bilateral chronic subdural collections (preferred term subdural hygroma, moderate in severity), and new left frontal area of hemosiderin measuring 4 mm on the right and 3 mm on the left side in the frontal regions. On the same day, and 15 days after the administration of the third dose of donanemab, the patient was diagnosed with the AE of moderate ARIA-H. Four days later, the participant experienced the AE of myoclonic jerks and was hospitalized for the SAE of seizure. The patient was treated with levetiracetam and recovered from the events of myoclonus and seizure on the same day. Study drug was withdrawn due to the event of ARIA-H. The final dose of study drug was on Study Day 57. Forty-nine days after the final dose, the patient experienced the SAE of severe subdural hematoma (worsening right subdural hematoma). A follow up CT scan 8 days later showed bleeding. The patient was hospitalized that day and underwent evacuation of the hematoma the following day. The AEs of headache and ARIA-H were reported as resolving at the time of the data cutoff and the subdural hematoma was considered not resolved.

Reviewer comment: A role for donanemab in the SAE of seizure could not be established because of the concurrent events of subarachnoid bleed and subdural hygroma, which were likely contributory. A role for donanemab in the event of subarachnoid bleed cannot be established because of the preceding events of fall, which were likely contributory. A role for donanemab in the AE of subdural hygroma and SAE of subdural hematoma cannot be established given the preceding event of fall, which is a risk factor for these AEs.

Hypersensitivity and Infusion Related Reaction

Nine SAEs related to the topic of hypersensitivity and infusion related reaction were reported in nine participants in Phase 2 and 3 studies while on treatment with donanemab or within 57 days of treatment.

Three of the nine SAEs related to the topic of hypersensitivity and infusion related reaction had the preferred term anaphylactic reaction (I5T-MC-AACI- (b) (6) I5T-MC-AACI- (b) (6) and I5T-MC-AACI- (b) (6)). The reviewer assessed two of the three cases as likely anaphylactic reactions (I5T-MC-AACI- (b) (6) and I5T-MC-AACI- (b) (6)) and the third case as a possible anaphylactic reaction (I5T-MC-AACI- (b) (6)). Of note, the reviewer

identified two additional cases as likely anaphylactic reaction (I5T-MC-AACI- (b) (6) and I5T-MC-AACI- (b) (6)). Both of the cases were not categorized as SAEs. One of the cases had the preferred term of anaphylactic reaction (I5T-MC-AACI (b) (6)) and the other infusion related reaction (I5T-MC-AACI- (b) (6)). The reader is referred to the Hypersensitivity and Infusion Related Reactions section of this review for further details in these cases.

The reviewer summarizes the three SAEs of anaphylactic reaction here.

Additionally, this reviewer notes an SAE of syncope that likely represents an infusion related reaction (I5T-MC-AACI- (b) (6)) summarized in the syncope section of narratives of SAEs, and an SAE of toxic metabolic encephalopathy that is possibly related and is summarized in the encephalopathy/mental status change section of narratives of SAEs (I5T-MC-AACG- (b) (6)). Cases with preferred terms of infusion related reaction, anaphylactic reaction and drug eruption are summarized here.

Anaphylactic reaction, I5T-MC-AACI- (b) (6)
72-year-old female with PMH of AD, hypercholesterolemia, history of anaphylactic reaction (cefotiam hydrochloride and penicillin) who received her second dose of donanemab and within 5 minutes of starting the infusion developed difficulty breathing and palpitations on Study Day 29.²⁴ The donanemab infusion was interrupted 15 minutes after starting, and she developed diarrhea, vomiting, weakness of the limbs, and hypotension. Her blood pressure was 88/57 mmHg and her heart rate was 93 beats per minute. Prior to the infusion, her blood pressure was 122/56 mmHg and her heart rate was 69 beats per minute. She was treated with epinephrine and calcium chloride/potassium/sodium chloride/sodium lactate that day and was admitted to the hospital overnight for observation. The SAE of moderate anaphylactic reaction was reported as resolved the following day and she was discharged from the hospital. The study drug was discontinued.

Reviewer comment: The case appears consistent with a diagnosis of anaphylactic reaction, given onset of vomiting and hypotension within minutes of a donanemab infusion. A role for donanemab is likely given temporal association.

Anaphylactic reaction, I5T-MC-AACI- (b) (6)
63-year-old female with history of AD, anxiety, migraine, hypothyroidism on levothyroxine who developed mucocutaneous urticaria, swelling and erythema of neck, throat and chest tightness, dry cough, and bronchospasm (noted on auscultation) 25 minutes after receiving the first donanemab infusion and was diagnosed with a moderate anaphylactic reaction. She was treated with diphenhydramine, epinephrine, methylprednisolone, and oral famotidine.

²⁴ Narrative updated by the sponsor to include history of anaphylactic reaction in a response dated August 19, 2022, to an information request dated August 17, 2022.

Approximately one hour after starting the donanemab infusion, her blood pressure was 163/82 mmHg and heart rate was 68 beats per minute (prior to the infusion, blood pressure: 137/77 mmHg, heart rate: 83 beats per minute [bpm]) and the urticaria and bronchospasm had resolved. She was taken to the ER and an exam showed blood pressure of 164/70 mmHg, heart rate 96 bpm, respiratory rate of 20 breaths/minute, shallow breathing, and an area of erythema on her neck. No labs or other diagnostic tests were performed. She was discharged as recovered and prescribed diphenhydramine, prednisone, and an epinephrine pen as needed.²⁵ The SAE was considered resolved on the same day, and she permanently discontinued from study drug and the study.

Reviewer comment: The case is consistent with anaphylaxis given onset of skin and mucosal involvement within minutes of exposure to the first infusion of donanemab and evidence of bronchospasm on exam.²⁶ A role for donanemab in the SAE is likely given temporal association with onset of the AE and the donanemab infusion. The mechanism of action is likely non-IgE mediated given lack of previous exposure to donanemab.

Anaphylactic reaction, IST-MC-AACI- (b) (6)
75-year-old female with past medical history of drug intolerance (codeine, levofloxacin and sulfa), allergy to cats, eczema, seasonal allergic disorder, lactose intolerance, who developed generalized erythema (including the chest, abdomen, back, throat, lip, ear, and eyelid), chest tightness, tachycardia, elevated blood pressure, and nausea within 12 minutes into her 3rd donanemab infusion. The SAE was reported to be severe anaphylactic reaction and the infusion was interrupted. Her heart rate was 93 beats per minute and blood pressure was 171/99 mmHg 15 minutes after starting the infusion. She was given epinephrine, intravenous diphenhydramine, and a normal saline bolus. The SAE was considered resolved on the same day. She was given four doses of oral diphenhydramine to be taken every 6 hours and discontinued from the study drug and the study because of the SAE. Of note, she had experienced paresthesias on the same day as her second infusion of donanemab.

Reviewer comment: The case may represent anaphylaxis given onset within minutes of the infusion, involvement of the skin, and development of chest tightness. A role for donanemab in the SAE is likely given temporal association with onset of the AE and the donanemab infusion.

Six of the nine SAEs related to the topic of hypersensitivity and infusion related reaction were

²⁵ Narrative updated by the sponsor in a response dated August 19, 2022, to an information request dated August 17, 2022, to specify that a second event of anaphylactic reaction was not experienced by the patient as originally described in the submission.

²⁶ Sampson H, Munoz-Furlong A, Campbell R, et al. Second symposium on the definition and management of anaphylaxis: summary report-Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network Symposium. J Allergy Clin Immunol 2006; 117: 391-397.

related to infusion related reactions (preferred terms: infusion related reaction [n=5] and drug eruption). A role for donanemab was likely in all cases. One case likely representing a delayed reaction (drug eruption, I5T-MC-AACG- (b) (6)). The reviewer summarizes the cases here.

Infusion related reaction, I5T-MC-AACG- (b) (6)

A 75-year-old female with history of AD, hyperlipidemia, hypertension, aortic atherosclerosis, gastroesophageal reflux disease and high titer of treatment-emergent anti-drug antibodies (TE-ADA) (>20,480) who experienced a severe infusion reaction, characterized by the development of chest pressure that started between 30 minutes of onset of the infusion and up to 6 hours after the fourth dose of donanemab on Study Day 93 (onset of the AE was reported retrospectively). Two days later (Study Day 95), the patient was admitted to the hospital with chest pressure, negative troponins, and nonspecific ecg findings. The patient also experienced mild dizziness, mild asthenia, mild reflux, and mild urinary tract infection on the same day. The patient was treated with acetylsalicylic acid 324 mg chewed once, sodium chloride 1000 ml intravenously, magnesium hydroxide simethicone 50 mg orally once, and famotidine 20 mg intravenously once. The patient had elevated lipase levels (number not reported). A CT of the abdomen/pelvis with contrast showed atherosclerotic vascular calcifications, including in the coronary arteries. The chest x-ray showed no focal consolidation, no pleural effusion or pneumothorax, and a normal cardiomeastinal silhouette. The following day (Study Day 96), rest and stress myocardial perfusion scintigraphy with single-photon emission computed tomography showed no scintigraphic evidence of myocardial infarction or stress induced myocardial ischemia, normal left ventricular ejection fraction and no regional wall motion abnormality. The event of infusion reaction was assessed as a delayed infusion reaction. On that day, the patient recovered from the SAE of infusion related reaction and from the AEs of headache, dizziness, and asthenia. The AE of gastroesophageal reflux disease was not resolved. No action was taken with the study drug in response to the SAE of infusion related reaction. The patient went on to receive another dose of donanemab prior to completing the double-blind treatment period and no AEs of infusion related reaction were reported.

Also of note, on Study Day 29, anti-drug antibodies were detected at a titer of 1:160. On Study Day 93 (after the fourth dose of donanemab), the titer levels had increased to 1:81,920. On Study Day 120, the anti-drug antibody titer level had decreased to 1:40,960. On the same day, she discontinued the study drug due to the AE of mild nausea. She also experienced mild dizziness on that day. She was reported to have recovered from both the nausea and the dizziness that same day. On Study Day 175, the ADA titer had decreased to 1:5120 and by Study Day 364 to 1:2560.

Reviewer comment: The symptom of chest pressure appears consistent with a diagnosis of infusion related reaction given temporal association with donanemab infusion and lack of other etiologies including a normal chest x-ray and lack of evidence of cardiac ischemia on stress

testing. In addition, a high titer of treatment emergent ADA is supportive of the diagnosis. A role for donanemab in the event of infusion related reaction is likely given temporal association.

Infusion related reaction, I5T-MC-AACI- (b) (6)

81-year-old male with history of drug hypersensitivity (allergy to sulfa, opium, and polysporin), seasonal allergy, and allergic rhinitis who developed the SAE of moderate infusion related reaction characterized by low blood pressure of 90/40 mmHg (135/65 mmHg before infusion), chest pain, nausea/vomiting, chills, malaise, and difficulty breathing/dyspnea that started between 30 minutes to 6 hours after the end of his second dose of donanemab (Study Day 34). He was hospitalized and had recovered from the SAE the following day and was discharged. The patient went on to receive 2 more infusions and no further AEs were reported.

Reviewer comment: The case appears consistent with a diagnosis of anaphylaxis given symptoms of dyspnea and hypotension. A role for donanemab in the event of anaphylaxis is likely based on temporal association. Given absence of reoccurrence with two additional exposures, this case appears consistent with a non-IgE mediated reaction.

Infusion related reaction, I5T-MC-AACI- (b) (6)

73-year-old female with history of hypertension, hypercholesterolemia who experienced the SAE of moderate infusion related reaction, characterized by the development of a hot flushed feeling and nausea 6-7 minutes into the fourth dose of donanemab administration. The infusion was interrupted. The patient was reported to experience low blood pressure (value not reported), headache, nausea/vomiting, chills, and myalgia. She received treatment with ondansetron and epinephrine on that day. She also received paracetamol and cetirizine as prophylaxis on that day and the following day. The SAE was reported as resolved that day and the study drug was permanently discontinued because of the SAE of infusion related reaction. Of note, during the third dose, the patient developed lightheadedness and nausea 11 minutes into the infusion and the study drug was interrupted. The study drug was resumed and the patient was noted to have a drop in blood pressure (value not reported).

Reviewer comment: The case appears consistent with a diagnosis of infusion related reaction. A role for donanemab in the event of infusion related reaction is likely based on temporal association.

Infusion related reaction, Pneumonia, Atrial fibrillation, I5T-MC-AACG- (b) (6)

This is a 70-year-old female with history of drug sensitivity, anaphylactic reaction (trigger not reported), asthma, atrial fibrillation, chronic kidney disease, diabetes mellitus type 2, and colon cancer who experienced the SAEs of infusion related reaction (severe), pneumonia of moderate

severity, and atrial fibrillation of mild severity, which started on the same day as administration of the fourth dose of donanemab (Study Day 122). The patient also developed hypertension and nausea within 5 minutes of the start of the fourth infusion. Vital signs included blood pressure 220/70 mmHg, heart rate 72, and respirations 26. Concomitant medications included metformin, amlodipine, calcium carbonate, glimepiride, irbesartan, magnesium, metformin, metoprolol, and procaterol. The patient was reported to then become hypotensive in the act of standing (systolic blood pressure of 80 mmHg). The patient received a normal saline bolus and oral diphenhydramine. Fifteen minutes after hypotension was recorded, the blood pressure was recorded at 140 mmHg. The patient felt shortness of breath, nausea, and anxiety. Five minutes later, the blood pressure was 180/75 mmHg. The patient was taken to the ER and developed atrial fibrillation with rapid ventricular response (heart rate in the 150s). Abnormal labs in the ER showed low platelet count, low lymphocytes, low potassium, elevated creatinine, decreased glomerular filtration rate, elevated glucose, and elevated lactic acid (platelet count 135×10^3 [150-400], lymphocytes auto 0.5×10^3 [1.0-4.8], potassium (K) 3.4 mmol/L [3.5-5.3], creatinine 1.2 mg/dL [0.5-1.1], estimated GFR 45L (≤ 60 ml/min), glucose 272 mg/dL [fast less than 100], and lactic acid 4.0 mmol/L [0.5-2.2]). She was started on a diltiazem drip for the atrial fibrillation and the dose of metoprolol succinate was increased. A CT scan of the chest showed the possibility of pneumonia versus an infiltrate or reaction to the drug. The patient was diagnosed with the SAE of pneumonia and was started on an antibiotic (name of antibiotic not reported). The metformin was discontinued because of lactic acidosis. Three days later (Study Day 125), the potassium was normal (4.1 mmol/L). The following day, the creatinine, lactic acid, lymphocyte count, and platelet count were normal (creatinine 1.0 mg/dL, lactic acid 1.9 mmol/L, lymphocyte count 1.1×10^3 , and platelet count 151×10^3). She was discharged on levofloxacin and diltiazem. She was also started on apixaban by her cardiologist. The SAEs of infusion related reaction and atrial fibrillation were considered recovered on Study Day 126 and the SAE of pneumonia on Study Day 130. On Study Day 148, the patient discontinued from study drug because of the SAE of infusion related reaction.

Reviewer comment: The case appears consistent with anaphylaxis given hypotension and symptoms of dyspnea. A role for donanemab in the SAE of infusion reaction is likely given temporal association of symptoms with infusion. The case is notable because of the documented elevated blood pressure of 220/70 mmHg and low blood pressure (systolic of 80 mmHg upon standing) that occurred at the time of the infusion related reaction. A role for donanemab in the SAEs of atrial fibrillation and pneumonia cannot be established given the concurrent event of infusion related reaction, which was likely contributory to the SAEs of atrial fibrillation and pneumonia. Additionally, the patient had a history of atrial fibrillation, which is likely a contributory factor to the development of atrial fibrillation.

Infusion Related Reaction, I5T-MC-AACI- (b) (6)

77-year-old female with hypertension, hyperlipidemia, and history of eyelid ptosis who

developed the SAE of infusion related reaction (mild in severity) on the day of the first dose of donanemab.²⁷ The patient reported the symptom of eyelid edema within 30 minutes of the end of study drug administration. The patient was taken to the ER for stroke evaluation after reporting worsening of eyelid ptosis, unsteady gait, and dizziness. An MRI of the brain showed no acute infarct or hemorrhage and symptoms were considered secondary to chronic ischemic changes and edema in the left masticator space. The symptoms of eyelid swelling resolved on the same day without treatment. She received a second dose of study drug and did not report any AEs related to infusion related reaction.

Reviewer comment: A role for donanemab in the SAE of infusion related reaction is likely given temporal association of symptom with infusion. This likely represents a non-IgE mediated reaction given occurrence after the first dose of donanemab.

Drug Eruption, IST-MC-AACG- (b) (6)

A 73-year-old female with history of allergy to tetanus vaccine, drug hypersensitivity (ibuprofen; sulfonamides, gastrointestinal tolerance), and eczema who reported the SAE of drug eruption 9 days after the first infusion with donanemab (moderate in severity). The patient had generalized itching and erythematous rash/hives on her neck, trunk, and extremities. The rash was reported as an erythematous, blanching raised rash on her extremities and trunk with a pruritic pink and purple eruption on her neck and back that spread to her arms and legs. She denied any eye irritation, oral lesions, or vaginal irritation. She denied any new exposures to food, detergents, soaps, and other body care products. She was seen in the ER and treated with prednisone and triamcinolone cream and diagnosed with a drug eruption. In the ER, her blood pressure was 146/72 mmHg, heart rate of 66 bpm, temperature 97.8 degrees Fahrenheit, respiratory rate 18 breaths per minute, and peripheral oxygen capillary saturation of 99%. On Study Day 13, she had a normal urinalysis (no blood or protein on microscopic examination), normal blood urea nitrogen (BUN) (21mg/dL with normal range 6-24), normal creatinine (0.82mg/dL with reference range of 0.44-1.03), normal complete blood count (CBC) (white blood cell count (WBC) 7.6 x10⁹/L [3.5-11.0], hemoglobin 12.4g/dL [11.0-15.0], and platelets 219 x10⁹/L [150-400]). The differential on the white count included neutrophils 81.2%, lymphocytes 12.3%, monocytes 5.0%, eosinophils 1.0%, absolute eosinophil count 0.1 K/uL (0.0-0.5), and basophils 0.5% (no reference ranges provided). The patient was evaluated by a dermatologist who described the skin exam on Study Day 13 that included lichenoid plaques on the bilateral ventral forearms, distal arms, thigh and shins with clearing in the abdomen, back and face. The dermatologist assessment was "favor drug eruption." Concomitant medications included warfarin (started > 15 years ago), iron, estradiol, memantine, calcium carbonate + D3. She was started on prednisone 60 mg daily for four days

²⁷ The AE of Localized edema was updated to the SAE of infusion related reaction in the 90-Day Safety Update, submission date August 17, 2022.

and the event resolved on Study Day 30. She withdrew from the study drug because of the SAE of drug eruption.

Reviewer comment: The case appears consistent with a diagnosis of a delayed hypersensitivity reaction. A role for donanemab in the event of drug eruption is likely given temporal association of drug with onset of symptoms. The case appears consistent with a non-IgE mediated reaction given occurrence after the first dose.

Pericardial effusion

One SAE of pericardial effusion was reported in one participant while on treatment with donanemab. A role for donanemab in the case was unlikely based likely chronicity of the pericardial effusion suggested by imaging and pathology. SAEs of pneumonia and pulmonary embolism were also reported in this case and a role for donanemab could not be established because of potential contributory factors of recent surgery for the pericardial effusion. The case is summarized here.

Pneumonia, pericardial effusion, pulmonary embolism, I5T-MC-AACN- (b) (6)

A 75-year-old male with history of hypothyroidism, hypertension, diabetes mellitus, developed mild shortness of breath on Study Day 21, 15 days after the first dose of donanemab, and was diagnosed with a moderate pericardial effusion with chronic inflammation based on results of a CT performed in the ER. The patient was hospitalized with the SAE of moderate pericardial effusion. On admission, the patient's blood pressure was 114/78 mmHg, heart rate of 115 beats per minute, leukocyte were 15 (units and reference range not reported), and platelets were 380 (units and reference range not reported), and international normalized ratio was 1.3 (reference range not available). An ecg showed sinus tachycardia, a chest x-ray showed cardiomegaly, and an echocardiogram confirmed effusion. The patient underwent an anterior pericardial window for evacuation of pericardial effusion and 950 ml was removed. The patient was reported to have a high leukocyte count throughout the hospitalization (value not reported), Covid-19 test was negative, ANA was negative and c-reactive protein was elevated at 1.01 (units and reference range not reported). On Study Day 23, he was diagnosed with a mild urinary tract infection and received ciprofloxacin. On Study Day 24, the drain was removed and he was discharged. The investigator reported that the etiology of the pericardial effusion was unclear and that the pathology report indicated no malignancy and that the fragments of pericardium had chronic inflammation. There was no evidence of B-cell or T-cell lymphoma on cytometry. The study drug was interrupted due to the SAE of pericardial effusion. On Study Day 30, the AE of urinary tract infection was reported as resolved. On Study Day 41, the patient was hospitalized with symptoms of heavy breathing, chest pain, and leg weakness. Oxygen saturation as 95%, blood pressure was 132/71 mmHg, peripheral pulse rate was 115 beats per minute, and the leukocyte count was high (value not reported). A CT angiography of the chest showed acute pulmonary embolism, mild cardiomegaly, and moderate pericardial effusion and

the patient was diagnosed with the SAEs of pulmonary embolism and pneumonia, both moderate in severity. The type of pneumonia was reported as secondary to pulmonary embolism. A CT of the head was normal. Venous duplex of bilateral lower extremities showed no evidence of deep vein thrombosis and an abdominal CT showed a left basilar effusion. A Covid-19 test was negative. Peripheral blood screening did not show evidence of B- or T-cell non-Hodgkin's lymphoma or leukemia. The event of pulmonary embolism was thought likely secondary to the pericardial window surgery and immobility. The effusion was thought secondary to prior Covid-19 infection that he had had ~ 1 year and 9 months prior to the first hospitalization. He was treated with apixaban and intravenous heparin and was discharged on Study Day 47. Study drug was permanently discontinued due to the SAE of pulmonary embolism.

Reviewer comment: A role for donanemab in the SAE of pericardial effusion is unlikely based on the pathology and CT findings of chronicity of the pericardial effusion. A role for donanemab in the SAEs of pulmonary embolism and pneumonia cannot be established because of the potential contributory factors of recent hospitalization and surgery for pericardial effusion, which are potential risk factors for development of pulmonary embolism and pneumonia.

Pneumonia

Seven SAEs of pneumonia were reported in seven participants in Phase 2 and 3 studies while on treatment with donanemab or within 57 days of treatment (preferred term: pneumonia). A role for donanemab in the seven cases could not be established in these cases because of underlying risk factors. All cases had age as a risk factor for pneumonia (age range of 70 years to 85 years) and five of the seven cases had dementia as a risk factor. Five of the six cases have additional potential contributory factors (recent hospitalization and thoracic surgery/I5T-MC-AACN-(b) (6) concurrent event of infusion related reaction/I5T-MC-AACG-(b) (6) vomiting/AE I5T-MC-AACG-(b) (6) chronic obstructive pulmonary disease/I5T-MC-AACG-(b) (6) and I5T-MC-AACG-(b) (6) and rib fractures secondary to a fall while playing with a pet/I5T-MC-AACN-(b) (6)). In the one case of pneumonia with fatal outcome, age (85 years) and moderate dementia were risk factors for pneumonia (I5T-MC-AACG-(b) (6)).

Pulmonary Embolism

Three SAEs of pulmonary embolism were reported in three participants in Phase 2 and 3 studies while on treatment with donanemab or within 57 days of treatment. In two cases, a role for donanemab could not be established because of underlying risk factors of hospitalization and recent surgery (I5T-MC-AACN-(b) (6) and I5T-MC-AACI-(b) (6)). In the third case, a role for donanemab was unlikely given that the patient had received 13 doses of donanemab prior to the onset of the SAE. I summarize the case here.

Pulmonary embolism, I5T-MC-AACG-(b) (6)
85-year-old male with history of AD, hypertension, peripheral edema, and peripheral venous

disease who presented to the ER with chest pain and generalized weakness and was hospitalized for the SAE of pulmonary embolism on Study Day 337, which occurred four days after his 13th dose. A CT of the head was normal. A CT of the chest indicated a non-occlusive pulmonary embolism within the right lower lobe and atelectasis-pneumonia in the left lower lobe with a small left pleural effusion. Concomitant medication included acetylsalicylic acid, amlodipine, vitamin D3, donepezil, dorzolamide, fish oil, hydrochlorothiazide, latanoprost, losartan, monascus purpureus, triamterene, trospium, q10, and vitamins NOS. The patient was discharged on Study Day 345 and was started on rivaroxaban the following day. The SAE of pulmonary embolism was reported as not recovered/not resolved at study completion.

Reviewer comment: Although a role for donanemab in the SAE of pulmonary embolism cannot be ruled out given that onset occurred while the patient was exposed to donanemab, factors not supportive of a causal link include that the patient had received 13 doses of study drug prior to onset of the AE.

Syncope

Nine SAEs of syncope were reported in eight participants in Phase 2 and 3 studies while on treatment with donanemab or within 57 days of treatment. Four of the eight cases had concurrent events that were likely contributory (SAE of anemia in a patient with history of anemia/I5T-MC-AACG- (b) (6) SAE of gastrointestinal hemorrhage in setting of apixaban use/I5T-MC-AACG- (b) (6) SAE of dehydration/I5T-MC-AACI- (b) (6) and SAE of acute myocardial infarction/I5T-MC-AACI- (b) (6)). Two cases of the eight cases had the likely contributory factor of history of syncope (history of intermittent syncope due to atrial fibrillation/I5T-MC-AACI- (b) (6) and history of syncope/I5T-MC-AACI- (b) (6)). In one of the eight cases, this reviewer could not establish a role for donanemab in the SAE of syncope as it occurred 17 days after the most recent dose of donanemab (I5T-MC-AACI- (b) (6)). In the remaining case, a role for donanemab was likely given onset during an infusion. I summarize the case here.

Syncope, I5T-MC-AACI- (b) (6)

A 78-year-old male with history of asthma, diabetes mellitus type 2, hypertension, and tobacco use who developed SAE of syncope on Study Day 91, on the same day as the fourth dose of donanemab. On Study Day 31, one day after receiving his second dose of donanemab, he experienced an AE of mild infusion related reaction, characterized by confusion, dizziness, and chills. The AE resolved two days later. On Study Day 63 and on the same day as his third infusion, he experienced a mild infusion related reaction, characterized by chills and shortness of breath. The infusion was interrupted on that day and received paracetamol and diphenhydramine. On Study Day 91, within five minutes of starting the fourth infusion, the patient passed out and was not responsive for three to five minutes. The patient's eyes were rolled back in his head, and no twitching, incontinence, or respiratory distress was observed.

Blood pressure upon waking was 144/98 mmHg and heart rate was 89 beats per minute and oxygen saturation was 93% (preinfusion: blood pressure: 140/82 mmHg and heart rate: 83 beats per minute). By the time the patient had arrived in the ER, his symptom had resolved. He denied any associated symptoms of chest pain, abdominal pain, nausea, vomiting, fever, chills, shortness of breath, headache, or dizziness. He was hospitalized and his diagnostic tests showed an elevated serum glucose of 231 mg/dL (reference range: 65-99 mg/dL), normal ECG, normal sodium and troponin-I (sodium 133 mmol/L [reference range: 136-145 mmol/L], troponin-I 23.1 ng/L [reference range: ≤ 78.5 ng/L]). A head CT showed no acute intracranial findings. A CT of the chest showed a mass within the upper lobe of the left lung. A biopsy was performed and showed moderate to poorly differentiated squamous cell carcinoma and the patient was diagnosed with the AE of moderate squamous cell carcinoma of the lung. On Study Day 94, the patient recovered from the event of syncope and was discharged. The patient permanently discontinued the study drug and study because of the SAE of syncope.

Reviewer comment: Although no other symptoms were reported with the syncopal event and low blood pressure was not documented, the SAE of syncope may represent a case of anaphylaxis given occurrence within minutes of the onset of the infusion. A role for donanemab in the SAE of syncope is likely given occurrence at the onset of infusion as well as the participant's previous infusion related reactions with previous donanemab doses. A role for donanemab in the AE of squamous cell carcinoma of the lung is unlikely given occurrence within 3 months of starting donanemab and given the patient's history of tobacco use was likely risk factor.

Arrhythmias

Nine SAEs related to arrhythmia were reported in nine participants in Phase 2 and 3 studies while on treatment with donanemab or within 57 days of treatment. Preferred terms included atrial fibrillation (n=5), atrial flutter, sinus node dysfunction, supraventricular tachycardia, and bradycardia. In eight cases, a role for donanemab could not be established because of the presence of risk factors for the arrhythmias (history of atrial fibrillation in the SAE of sinus node dysfunction/I5T-MC-AACG- (b) (6) history of atrial fibrillation in the SAEs of atrial fibrillation or atrial flutter/ I5T-MC-AACI- (b) (6) I5T-MC-AACI- (b) (6) I5T-MC-AACI- (b) (6) and I5T-MC-AACI (b) (6) abdominal surgery one day prior to the SAE of atrial fibrillation/I5T-MC-AACI- (b) (6) history of coronary artery disease and cardiomyopathy in the SAE of supraventricular tachycardia/I5T-MC-AACI- (b) (6) and history of dyslipidemia, aortic arteriosclerosis in the SAE of atrial fibrillation/I5T-MC-AACI- (b) (6)). In the remaining case, a role for donanemab could not be established in the SAE of bradycardia, as the patient went on to receive three additional doses of donanemab without reoccurrence (I5T-MC-AACI- (b) (6)). The case is summarized here.

SAEs of bradycardia and dehydration, I5T-MC-AACI- (b) (6)

A 79-year-old female with medical history of hypothyroidism, hypercholesterolemia, hypertension, depression, and anxiety was hospitalized for the SAEs of bradycardia (moderate in severity, value not reported), dehydration (moderate in severity), hypotension and syncope on Study Day 72, 13 days after the third dose of donanemab.²⁸ Abnormal laboratory tests included an elevated blood sugar of 158 (units not provided, reference range 74-106), elevated blood urea of 31 (units not provided, reference range 7-17), and blood urea nitrogen/creatinine ratio 34 (reference range 10-20). Results of a CT of the brain, echocardiogram, chest x-ray, and ECG were reported as normal. The cause of the syncopal event was attributed to dehydration and the cause of dehydration was attributed to a lack of intake of water. The TSH was normal at 1.62 (units not provided, reference range 0.470- 4.680). She received one liter of normal saline. She was discharged on Study Day 77. Concomitant medications included atenolol (ongoing for at least 5 years). Prior to the SAE of bradycardia, the patient had a normal blood pressure of 122/66 mmHg and pulse rate of 62 beats per minute (recorded on Study Day 60). The participant went on to receive three additional doses of donanemab and did not experience any AEs of bradycardia or syncope.

Reviewer comment: A role for donanemab in the SAEs of bradycardia and dehydration and the AE of syncope cannot be established given that the event occurred 13 days after the most recent dose and did not reoccur after receiving three additional doses of donanemab.

Infections

Twenty SAEs related to infection were reported in 19 participants in Phase 2 and 3 Studies while on treatment with donanemab or within 57 days of treatment.²⁹ Preferred terms included pneumonia (n=7), diverticulitis (n=3), salmonellosis (n=2, both occurring in one participant), bacterial arthritis, bacterial sepsis, gastroenteritis, kidney infection, peritoneal abscess, peritonitis, aspiration pneumonia, and sepsis.

In the three cases of diverticulitis, a role for donanemab could not be ruled out because temporal proximity with onset of the SAE and the first dose of donanemab (21 to 41 days from the first dose). Risk factors existed in the cases including diverticulosis (I5T-MC-AACI- (b) (6) and I5T-MC-AACI- (b) (6)) and concomitant medications associated with risk for diverticulitis (acetylsalicylic acid/I5T-MC-AACI- (b) (6) and diclofenac/I5T-MC-AACN- (b) (6) (b) (6)).³⁰

²⁸ Additional details of the narratives are noted in the sponsor's response dated October 24, 2022, to an information request dated October 21, 2022.

²⁹ At the time of the 90-Day Safety Update, the SAE of abscess rupture had been updated to large intestine perforation (I5T-MC-AACI- (b) (6)).

³⁰ Peery A, Shaukat A, Strate L. AGA Clinical Practice Update on Medical Management of Colonic Diverticulitis: Expert Review. *Gastroenterology*. 2021 Feb;160(3):906-911.e1. doi: 10.1053/j.gastro.2020.09.059.

In the remaining cases of infection, a role for donanemab could not be established, because of concurrent events, past medical history, or concomitant medication use.

The seven SAEs with preferred term of pneumonia are discussed in the pneumonia section of SAE narratives. A role for donanemab in the seven cases could not be established because of underlying risk factors. A role for donanemab could not be established in one SAE of aspiration pneumonia, because of the preceding event of aspiration during an endoscopy procedure (I5T-MC-AACI- (b) (6)).

In the case of bacterial sepsis and the case of sepsis, a role for donanemab could not be established because of underlying risk factors and concurrent events. Risk factors for bacterial sepsis included medical history of diabetes mellitus and concurrent event of urinary tract infection (I5T-MC-AACG- (b) (6)). In the same case, a role for donanemab in the event of urinary tract infection could not be established because of concomitant medication use with mirabegron and simvastatin, which are associated with risk for urinary tract infection.^{31,32} In the case of sepsis, past medical history of diabetes was a risk factor (I5T-MC-AACN- (b) (6)).

In one case with SAEs of salmonellosis, a source could not be identified; however, a likely risk factor for salmonellosis in general is exposure to contaminated food and a role for donanemab in the case was unlikely (I5T-MC-AACI- (b) (6)).³³

A role for donanemab in the SAE of gastroenteritis could not be established as the event occurred after nine doses of donanemab and the patient went on to receive nine additional doses without experiencing any AEs (I5T-MC-AACG- (b) (6)).

In the additional SAEs, the reviewer did not establish a role for donanemab in the SAEs because of risk factors (kidney stones for the SAE of kidney infection/I5T-MC-AACI- (b) (6) large intestine perforation due to adenocarcinoma of the colon [diagnosed 41 days after first dose of donanemab] for the SAE of peritonitis/I5T-MC-AACI- (b) (6) patella fracture for the SAE of bacterial arthritis/I5T-MC-AACI- (b) (6) and history of peritoneal abscess for the SAE of peritoneal abscess/I5T-MC-AACI- (b) (6)).

In Phase I studies, two SAEs of urinary tract infection were reported in two participants. In one

³¹ Myrbetriq. Labeling-Prescribing Information. Drugs@fda.gov. Action date March 25, 2021. Accessed August 22, 2022.

³² Zocor. Labeling-Prescribing Information. Drugs@fda.gov. Action date May 31, 2022. Accessed August 22, 2022.

³³ Centers for Disease Control and Prevention, National Center for Emerging and Zoonotic Infectious Diseases (NCEZID), Division of Foodborne, Waterborne, and Environmental Diseases (DFWED). Salmonella. Information for Healthcare Professionals and Laboratories. <https://www.cdc.gov/salmonella/general/technical.html> Last reviewed July 18, 2022. Accessed August 23, 2022.

case, a role for donanemab could not be established because of underlying risk factors including past medical history of benign prostatic hypertrophy and hypertonic bladder (AACG- (b) (6)). In the second case, a role could not be established given onset 485 days after the first dose of donanemab (AACD- (b) (6)).

Fall

Seven SAEs with preferred term of fall were reported in six participants in Phase 2 and 3 Studies while on treatment with donanemab or within 57 days of treatment. A role for donanemab in the SAEs of falls could not be established in six of the SAEs because of underlying risk factors. Risk factors included medical history (peripheral neuropathy, lumbar spinal stenosis, BPPV/I5T-MC-AACG- (b) (6)) and concurrent events (fall while playing softball/I5T-MC-AACI- (b) (6), (b) (6) poor fluid intake, urinary tract infection, Klebsiella pneumonia, Covid infection/I5T-MC-AACI- (b) (6) fall from ladder/I5T-MC-AACI- (b) (6) fall after playing with pet cat and fall after recent diagnosis of rib fracture/I5T-MC-AACN- (b) (6)). A role for donanemab in the seventh case of fall could not be established because of potential contributory factors including event of moderate syncope on the same day (I5T-MC-AACI- (b) (6)). In this case, the participant had six additional doses of donanemab and did not experience any additional AEs of fall or syncope.

Dehydration

Five SAEs with preferred term of dehydration were reported in five participants in Phase 2 and 3 Studies while on treatment with donanemab or within 57 days of treatment. A role for donanemab in the SAEs of dehydration could not be established in three of the five cases because of concurrent events including lack of eating on the day of the event (I5T-MC-AACG- (b) (6)), pneumonia and fall occurring the day prior to SAE (I5T-MC-AACG- (b) (6)), and report of poor oral intake (I5T-MC-AACG- (b) (6)). In the remaining two cases, this reviewer did not establish a role for donanemab in the events as they occurred 5 and 13 days after the last dose of donanemab (I5T-MC-AACI- (b) (6) and I5T-MC-AACI- (b) (6) respectively).

Fracture

Five SAEs related to fracture were reported in five participants in Phase 2 and 3 Studies while on treatment with donanemab or within 57 days of treatment. Preferred terms included rib fracture (n=3), femoral neck fracture, and wrist fracture. Two of the five cases had osteoporosis as risk factor (I5T-MC-AACI- (b) (6) and I5T-MC-AACI- (b) (6)). Two of the five cases had events preceding the fractures that were likely contributory (fall from ladder/I5T-MC-AACI- (b) (6) and playing with pet/I5T-MC-AACN- (b) (6)). The fifth case involved a 78-year-old female who developed SAEs of rib fracture and hemothorax 50 days after the first dose of donanemab and 22 days after the second dose (I5T-MC-AACI- (b) (6)). In this case, although the etiology for the fracture was unclear; the reviewer did not establish a role for donanemab as the case seemed consistent with the development of a spontaneous rib fracture in an elderly patient.

Encephalopathy/Mental status changes

Five SAEs related to the topic of encephalopathy and mental status changes in five participants in Phase 2 and 3 studies while on treatment with donanemab or within 57 days of treatment. Preferred terms included mental status change (n=2), encephalopathy, metabolic encephalopathy, and toxic encephalopathy. A role for donanemab in two cases could not be established because of concurrent events (Covid-19 infection/I5T-MC-AACI- (b) (6) and hypoxia and acute respiratory failure/I5T-MC-AACI- (b) (6)). A role for donanemab in the second case of mental status changes appeared unlikely because the event occurred 20 days after the fourth dose (I5T-MC-AACI- (b) (6)). A role for donanemab in the SAE of toxic encephalopathy was possible and the case is summarized here.

Toxic Encephalopathy, I5T-MC-AACG- (b) (6)

81-year-old female with past medical history of rectal cancer stage I, constipation, drug hypersensitivity (sulfa and niacin allergy), and chronic kidney disease who developed the SAE of toxic encephalopathy two days after the fourth dose of donanemab and 153 days after the first dose. Concomitant medications included acetylsalicylic acid, calcium carbonate, donepezil, fluocinonide cream, levothyroxine, loperamide, multivitamins, and simvastatin. On Study Day 108, an MRI of the brain obtained prior to the first donanemab infusion showed presence of cortical infarct in the right parietal lobe (unchanged). The patient had the first donanemab infusion on Study Day 152.

At baseline, the patient had a normal blood hemoglobin level at 7.13 mmol/L-Fe (reference range: 7.13-9.80 mmol/L-Fe) and a low blood erythrocytes level at 3.7×10^{12} cells/L (reference range: $3.9\text{-}5.5 \times 10^{12}$ cells/L) a normal creatinine at 114 $\mu\text{mol/L}$ (reference range: 31-128 $\mu\text{mol/L}$) and normal blood urea nitrogen at 7.1 mmol/L (reference range: 1.4-12.1 mmol/L). On Study Day 286, an MRI showed the presence of a cortical infarct in the right parietal lobe.

On Study Day 303, the patient's blood hemoglobin was low at 6.95 mmol/L-Fe and blood erythrocytes was low at 3.6×10^{12} cells/L. On this day, the dose of donanemab was increased to 1400 mg every four weeks. Vital signs preinfusion included blood pressure 169/81, heart rate 68 beats per minute, and temperature of 36.3 degrees Celsius. On the same day, the patient started experiencing worsening of mental status and weakness after the infusion. The following day (Study Day 304), the patient's mental status and weakness continued to worsen, and the AE of severe toxic encephalopathy (acute metabolic encephalopathy secondary to medication side effect) was reported. The patient was reported to be more confused, weak, unable to ambulate or move the legs, and had experienced some urinary incontinence since the study drug infusion.

On Study Day 306, the patient presented to the ER and was hospitalized for acute metabolic

encephalopathy secondary to medication side effect. Per the narrative, although it was not clearly known which metabolic derangement or medication led to encephalopathy, the diagnosis was made due to the timing of symptoms in relation to the administration of study drug and dose escalation.

The patient had normal vital signs (blood pressure 119/54 mmHg, body temperature was 98.5 degrees Fahrenheit, heart rate was 73 beats/minute, respiratory rate was 20 breaths/minute) and a normal physical exam except for mild epistaxis from the right nostril. The patient's blood creatinine was elevated at 1.3 mg/dL (reference range: 0.5- 0.9 mg/dL), blood sodium was normal at 135 mmol/L (reference range: 136- 145 mmol/L), glomerular filtration calculation was decreased at 39.21 mL/min (reference range: 60 mL/min), hematocrit was low at 33.1 % (reference range: 35-45%), red blood cell count was low at 3.61 μ L (reference range: 4-5 μ L), hemoglobin was low at 11.1 g/dL (reference range: 11.8-15.8 g/dL), white blood cell count was elevated at 11.4 μ L (reference range: 4.5-10.5 μ L) which reduced to 8.8 μ L. The lymphocyte percentage was low at 13 % (reference range: 16-46%), neutrophil percentage was elevated at 78 % (reference range: 44-74%), and C-reactive protein was 2.6 (reference range not available). The patient's metabolic panel and thyroid stimulating hormone levels were normal. The patient's urine analysis revealed presence of traces of leukocyte esterase (reference range: negative) and traces of leukocytes, and absence of nitrites. A head CT showed presence of chronic ischemic and involutional changes, and absence of acute intracranial abnormality. An ECG showed normal sinus rhythm and probability of left atrial enlargement. On Study Day 308, an MRI of the brain showed absence of acute infarct, mass, or lesion, and presence of chronic ischemic and involutional changes, small microhemorrhage in left temporal lobe (approximately 3mm) and a cavernoma.

On Study Day 309, the patient was reported to recover from the SAE of toxic encephalopathy with sequelae of increased confusion. The patient underwent physical and occupational rehabilitation following discharge. The action taken with study drug was reported as drug withdrawn due to the SAE of toxic encephalopathy. The patient permanently discontinued the study drug and treatment period due to the SAE of toxic encephalopathy.

Reviewer comment: A role for donanemab in the SAE of encephalopathy appears possible given onset of symptoms on the same day as the infusion. Although the SAE is noted as toxic metabolic encephalopathy, vital signs, labs, and imaging were unrevealing for the specific cause of encephalopathy.

In the fifth case, a role for donanemab in the SAE of encephalopathy (moderate in severity) was unlikely as the event occurred 27 days after the most recent dose of donanemab. The case is summarized here.

Encephalopathy, I5T-MC-AACG- (b) (6)

A 76-year-old male with medical history of atrial fibrillation, bradycardia, coronary artery disease, hyperlipidemia, hypertension, and pollakiuria who developed the SAE of encephalopathy (moderate in severity) 140 days after the first dose and 27 days after the fifth dose of donanemab. On Study Day 140, the patient presented to the ER after an episode of decreased responsiveness. Per the narrative, initial bloodwork showed no significant abnormalities and urine analysis showed no evidence of an infection. An MRI scan showed no evidence of a bleed or acute injury. A chest x-ray and head CT showed no acute findings. No epileptiform activity was detected on an encephalogram. Overnight telemetry showed no arrhythmias. The following day, the patient recovered from the encephalopathy and was discharged from the hospital with diagnosis of acute encephalopathy of unclear etiology. The patient went on to receive an additional 9 doses of donanemab. The patient experienced the AE of lethargy (mild in severity) on Study Day 202, 5 days after the most the most recent dose of donanemab, and headache (mild in severity) on Study Day 318, two days after the most recent dose of donanemab. Four hundred and eleven days after the last dose of donanemab, the patient experienced the SAE of death. The cause of death was unknown. This case is discussed further in the Deaths section of this review.

Reviewer comment: A role for donanemab in the event of encephalopathy is unlikely given that the event occurred 27 days after the most recent dose of donanemab and did not reoccur after the participant received nine additional doses of donanemab.

Suicide-related events

Four SAEs of suicide-related events were reported in four participants in Phase 2 and 3 Studies while on treatment with donanemab or within 57 days of treatment. Preferred terms included completed suicide (n=2), suicide attempt, and suicidal depression. Three of the four cases had fatal outcome and are summarized in the Deaths section of this review (completed suicide/I5T-MC-AACI- (b) (6) completed suicide/5T-MC-AACI- (b) (6) and suicide attempt I5T-MC-AACI- (b) (6)). A role for donanemab in these three cases could not be established as the SAEs were reported in participants of the main study of AACI where treatment was still blinded. In the fourth case, a role for donanemab in the event cannot be ruled out and the case is summarized here.

Suicidal depression, I5T-MC-AACI- (b) (6)

A 72-year-old male with AD, hypertension, rheumatoid arthritis, low back pain, and no psychiatric medical history experienced the SAE of suicidal depression 31 days after the first dose of donanemab. Concomitant medications included apoeaquorin, atorvastatin, cefalexin, celecoxib, hydrochlorothiazide, multivitamin, triamterene, and vitamin D. The patient had been on all concomitant medications for at least a year, except for cefalexin which was started on Study Day - 8 for the AE of bilaterally lower leg cellulitis reported on the same day. At baseline,

the patient's Columbia Suicide Severity Rating Scale (C-SSRS) responses showed no events of suicidal ideation and suicidal behavior; no self-harm events were reported. On Study Day 31, the patient became violent, threatened to stab himself with a knife, and was hospitalized for the SAE of moderate suicidal depression. The most recent dose had been 30 days before. The patient was reported to be agitated, anxious upon arrival, and required chemical restraints. A chest x-ray obtained that day showed mild cardiomegaly. He was evaluated by a psychiatrist who noted that the patient was stressed due to current living situations and financial difficulty. The patient had not taken antidepressant or antipsychotic medications before. He received treatment with lorazepam the same day. He was discharged from the hospital five days later and the SAE of suicidal depression was considered recovered. The following day (Study Day 37), he experienced the AE of moderate depression and was started on treatment with citalopram, risperidone, and thiamine. On Study Day 50, he received the second dose of donanemab. On the same day, the patient's C-SSRS responses showed no events of suicidal ideation and suicidal behavior; no self-harm events were reported. On Study Day 65, the patient was reported to have had a violent episode (further details not reported). A psychiatric evaluation noted that the patient did not have any intention to harm himself or threaten others. He received the third and fourth dose of donanemab on Study Days 72 and 90. The patient's C-SSRS responses on those days showed no events of suicidal ideation and suicidal behavior; no self-harm events were reported. The AEs of depression was reported as not resolved at the time of data cut-off. MRIs on Study Days 24 and 80 and at baseline showed no evidence of ARIA. Prior to the data cut-off, he received the fifth dose of medication on Study Day 114.

Reviewer comment: A role for donanemab in the SAE of suicidal depression cannot be ruled out given temporal association with onset of the SAE of suicidal depression and infusion of donanemab. Other possible etiologies for suicidal depression include worsening AD and life stressors, including living situation and finances.

Diabetic Ketoacidosis

One SAE of diabetic ketoacidosis was reported on one donanemab-treated participant with diabetes mellitus type 1 in Phase 2 and 3 Studies (I5T-MC-AACG- (b) (6)). The SAE occurred 110 days after the first dose of donanemab and 54 days after the third dose, which was the most recent dose. The reviewer did not identify a role for donanemab in the SAE because the onset of the event occurred close to five-times the half-life of donanemab, when exposure to donanemab would be low.

Acute Kidney Injury

One SAE of acute kidney injury was reported in one participant in Phase 2 and 3 Studies while on treatment with donanemab or within 57 days of treatment (I5T-MC-AACI- (b) (6)). The SAE occurred 51 days after the first dose of donanemab and 23 days after the second dose. The reviewer did not establish a role for donanemab in the SAE because the concurrent events of pneumothorax and multiple rib fractures, which were likely contributory.

Acute respiratory failure

One SAE of acute respiratory failure was reported on one donanemab-treated participant in Phase 2 and 3 Studies while on treatment or within 57 days of treatment (IST-MC-AACI- (b) (6)). In this case, a role for donanemab could not be established in the SAE with fatal outcome because risk factors for acute respiratory failure existed in the case including multifocal pneumonia and a medical history of chronic obstructive pulmonary disease. The reader is referred to the Deaths section of this review for further the narrative for this participant.

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

Adverse events reported to lead to study withdrawal occurred with higher frequency in the donanemab arm compared to placebo in Study AACG (15% versus 5%, respectively). The most frequent TEAEs reported to lead to study withdrawal in Study AACG were allergic reaction/hypersensitivity and ARIA-H microhemorrhage. TEAEs reported to lead to study withdrawal with highest frequency in the all-donanemab pool at the time of the 90-Day Safety Update included allergic reaction/hypersensitivity and ARIA-E.

Adverse events reported to lead to treatment discontinuation occurred with higher frequency in the donanemab arm compared to placebo in Study AACG (31% versus 7%, respectively). Adverse events leading to treatment discontinuation for ARIA and infusion related reactions/systemic hypersensitivity reactions were driven by protocol in Phase 2 and 3 studies. The most frequent TEAEs reported to lead to treatment discontinuation in Study AACG were allergic reaction/hypersensitivity, ARIA-E, and ARIA-H Superficial Siderosis. TEAEs reported to lead to treatment discontinuation with highest frequency in the all-donanemab pool included allergic reaction/hypersensitivity and ARIA-E.

Permanent treatment discontinuation with donanemab was indicated by protocol for events related to ARIA and for infusion reactions. The reader is referred to the ARIA section of this review for further details on conditions related to ARIA leading to permanent treatment discontinuation.

Overall, this reviewer found the sponsor's protocol for treatment discontinuation to be acceptable.

A similar frequency of participants discontinued from Study AACG in donanemab and placebo arms (28% and 26%, respectively). Adverse events leading to study withdrawal were reported in a higher frequency of participants in the donanemab arm compared to placebo (15% versus 5%, respectively). The following table shows disposition related to study withdrawal in Study AACG.

Table 13. Disposition Related to Study Withdrawal in Study AACG During the Treatment Period.

Disposition	Donanemab N=131 n (%)	Placebo N=125 n (%)
Completed	94 (72)	93 (74)
Discontinued	37 (28)	32 (26)
Adverse event	20 (15)	6 (5)
Death	1 (1)	2 (2)
Other	3 (2)	8 (6)
Physician decision	0	1 (1)
Protocol deviation	1 (1)	1 (1)
Withdrawal by participant	12 (9)	12 (10)
Withdrawal due to caregiver circumstances	0	2 (2)

The reviewer created this table using the IBD ADDS dataset, studyID = AACG, parameter = study disposition.

Allergic reaction/hypersensitivity were among the most frequently reported TEAEs leading to study withdrawal in Study AACG. The following table shows TEAEs leading to study withdrawal with frequency of at least 2% higher in the donanemab arm compared to placebo in Study AACG.

Table 14. TEAEs Reported to Lead to Study Withdrawal by Preferred and Grouped Terms with Frequency of at Least 2% Higher in the Donanemab Arm Compared to Placebo in Study AACG

Adverse Event	Donanemab N=131 n (%)	Placebo N=125 n (%)
Allergic Reaction and Hypersensitivity MQG	6 (5)	0
Infusion Related Reaction	5 (4)	0
Drug Eruption	1 (1)	0
ARIA-H Microhemorrhage ¹	3 (2)	0

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

MQG: MedDRA Query Group. The reviewer created this using the IDB ADAE dataset submitted 8.25.22, SAFFL = Yes, StudyID=AACG, PCIN57FL = Yes, TRTEMFL = Yes, DISAEFL=Yes. Of note, the number of participants with AEs reported to lead to study withdrawal in this table is not the same as the numbers reported in the previous table because of different time cuts. The previous table is based on up to 72-weeks in the treatment period, whereas this table is based on AEs occurring in the treatment period plus 57 days after the last dose of donanemab for the donanemab arm or placebo for the placebo arm.

At the time of the 90-Day Safety Update, 4% (56/1304) of participants in the all-donanemab pool reported TEAEs leading to study withdrawal. Allergic reaction/hypersensitivity and ARIA-E were among the most frequently reported TEAEs leading to study withdrawal. The following

table shows TEAEs reported to lead to study withdrawal by preferred term and groups of preferred terms with frequency of at least 1% in the all-donanemab group after the 90-Day Safety Update.

Table 15. TEAEs Reported to Lead to Study Withdrawal by Preferred and Grouped Terms with Frequency of at Least 1% in the All-Donanemab Group after the 90-Day Safety Update

Adverse Event	DON N=1304 n (%)
Allergic Reaction and Hypersensitivity MQG	25 (2)
Infusion Related Reaction	20 (2)
Anaphylactic Reaction	3 (<0.5)
Drug Eruption	1 (<0.5)
Hypersensitivity	1 (<0.5)
ARIA-E ¹	7 (1)

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

MQG: MedDRA Query Group. The reviewer created this using the IDB ADAE dataset submitted 8.25.22, SAFFL = Yes, TRT01A = inversion of Dona-C, SAFFL = Yes, LYIN57FL = Yes, TRTEMFL = yes, DISAEFL=Yes.

Treatment discontinuations related to TEAEs were reported at a higher frequency in the donanemab arm compared to placebo in Study AACG (31% versus 7%, respectively). A higher frequency of participants on placebo who discontinued treatment were recorded as “other” compared to the donanemab arm (16% versus 5%, respectively). A review of reported terms for discontinuation indicated “other” for the majority of patients in either arm. In a response dated August 4, 2022, to an information request dated July 29, 2022, the sponsor noted that although verbatim terms were not captured for participants who listed “other” as a reason for treatment discontinuation, many participants discontinued treatment in close temporal proximity to discontinuation of the study. For participants receiving placebo who discontinued the study and listed “other” as a reason for discontinuation, reasons included Covid-19 and study burden. The following table shows disposition related to treatment discontinuation in Study AACG.

Table 16. Disposition Related to Treatment Discontinuation in Study AACG During the Treatment Period

Disposition	Donanemab N=131 n (%)	Placebo N=125 n (%)
Completed	82 (63)	91 (73)
Discontinued	49 (37)	34 (27)
Adverse event	40 (31)	9 (7)

Disposition	Donanemab N=131 n (%)	Placebo N=125 n (%)
Death	0	1 (1)
Other	7 (5)	20 (16)
Physician decision	0	1 (1)
Protocol deviation	0	1 (1)
Withdrawal by participant	2 (2)	1 (1)
Withdrawal due to caregiver circumstances	0	1 (1)

The reviewer created this table using the IBD ADDS dataset, studyID = AACG, parameter = treatment disposition

Allergic reaction/hypersensitivity, ARIA-E, and ARIA-H Superficial Siderosis were the most frequently reported TEAEs leading to treatment discontinuation in Study AACG. The following table shows TEAEs reported to lead to treatment discontinuation in Study AACG with frequency of at least 2% higher in the donanemab arm compared to placebo.

Table 17. TEAEs Reported to Lead to Treatment Discontinuation by Preferred and Grouped Terms with Frequency of at Least 2% Higher in the Donanemab Arm Compared to Placebo in Study AACG

Adverse Event	DON N=131 n (%)	Placebo N=125 n (%)
Allergic Reaction and Hypersensitivity MQG	9 (7)	0
Infusion Related Reaction	7 (5)	0
Drug Eruption	1 (1)	0
Urticaria	1 (1)	0
ARIA-E ¹	7 (5)	1 (1)
ARIA-H Superficial Siderosis ¹	6 (5)	1 (1)
ARIA-H Microhemorrhage ¹	5 (4)	0

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

MQG: MedDRA Query Group. The reviewer created this using the IDB ADAE dataset submitted 8.25.22, SAFFL = Yes, StudyID=AACG, PCIN57FL = Yes, TRTEMFL = yes, DISTAEFL=Yes. Of note, the number of participants reporting AEs leading to treatment discontinuation in this table is not the same as the numbers reported in the previous table because of different time cuts. The previous table is based on up to 72-weeks in the treatment period, whereas this table is based on AEs occurring in the treatment period plus 57 days after the last dose of donanemab for the donanemab arm or placebo for the placebo arm.

At the time of the 90-Day Safety Update, 8% (100/1304) of participants in the all-donanemab pool reported TEAEs leading to treatment discontinuation. Allergic reaction/hypersensitivity and ARIA-E were among the most frequently reported TEAEs leading to treatment discontinuation. The following table shows TEAEs reported to lead to treatment discontinuation by preferred term and groups of preferred terms with frequency of at least 1% in the all-

donanemab group after the 90-Day Safety Update.

Table 18. TEAEs Reported to Lead to Treatment Discontinuation by Preferred and Grouped Terms with Frequency of at Least 1% in the All-Donanemab Group after the 90-Day Safety Update

Adverse Event	DON N=1304 n (%)
Allergic Reaction and Hypersensitivity MQG	41 (3)
Infusion Related Reaction	35 (3)
Anaphylactic Reaction	3 (<0.5)
Drug Eruption	1 (<0.5)
Hypersensitivity	1 (<0.5)
Urticaria	1 (<0.5)
ARIA-E ¹	19 (1)
ARIA-H Microhemorrhage ¹	13 (1)

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

MQG: MedDRA Query Group. The reviewer created this using the IDB ADAE dataset submitted 8.25.22, SAFFL = Yes, TRT01A = inversion of Dona-C, SAFFL = Yes, LYIN57FL = Yes, TRTEMFL = Yes, DISTAEFL=Yes.

Among BACE-I treated participants in Study AACG, AEs of superficial siderosis of the central nervous system (I5T-MC-AACG- (b) (6)) and subarachnoid hemorrhage (I5T-MC-AACG- (b) (6)) were reported to lead to treatment discontinuation and study withdrawal in two participants. The case of subarachnoid hemorrhage is discussed further in the Narratives section of the Serious Adverse Events section of this review.

Among the blinded safety population of Study AACI, 5.9% (102 participants) discontinued treatment due to an AE.³⁴ The most frequently reported AEs reported to lead to treatment discontinuation were infusion related reaction (1.3%) and ARIA-E (1.0%).

In Study AACG, one donanemab-treated participant withdrew from the study for the AE of infusion related reaction (dyspnea).

In Study AACD, two donanemab-treated participants withdrew from the study for AEs of hypertensive crisis (AACD- (b) (6)) and vasogenic cerebral edema (AACD- (b) (6)). In the case of vasogenic cerebral edema, a role for donanemab in the event was likely given onset on the day of onset of ARIA-E. The case is discussed further in the Narratives section of the Serious Adverse Events section of this review. In the case of hypertensive crisis, a role for donanemab

³⁴ Noted on page 55 of the sponsor's 90-Day Safety Update submitted August 17, 2022.

could not be ruled out and the case is summarized here.

AE of hypertensive emergency, AE of hypertensive crisis reported to lead to study withdrawal, AACD- (b) (6) 35

A 58-year-old female with cognitive disorder, amnesia, hypertension, depression, anxiety, anemia, low back pain and migraine who discontinued from the study for the event of hypertensive crisis (verbatim term: hypertensive urgency) of mild severity 169 days after the first dose of donanemab (20 mg/kg IV every 4 weeks). The participant experienced the AE of hypertensive emergency (moderate severity) 1 hour and 49 minutes after the start of the infusion. The blood pressure preinfusion was 173/94 mmHg and a pulse rate of 73 beats per minute. An unscheduled blood pressure was 150/90 mmHg and a pulse rate of 79 beats per minute. At the end of the infusion, the blood pressure was 174/101 mmHg and a pulse rate of 81 beats per minute. During the infusion, the patient also complained of a bilateral throbbing headache and lower back pain. The participant had a maximum value anti-drug antibody titer of 1:327680 on this day. The study medication was interrupted, and the event resolved 4 hours and 15 minutes after onset. The following day, the participant experienced hypertensive crisis (mild in severity). The following day, the patient's blood pressure was 200/99 mmHg and a pulse rate of 62 beats per minute. One hour and 40 minutes later, the blood pressure was 160/84 mmHg. Concomitant medications included escitalopram, axotal (aspirin/butalbital), Thomapyrin N (aspirin, acetaminophen, caffeine), ibuprofen, atorvastatin, hydrochlorothiazide, and paracetamol. The hydrochlorothiazide was discontinued and lisinopril was started on that day. The participant was discontinued from the study because of the adverse event of hypertensive crisis.

Reviewer comment: A role for donanemab in the AEs of hypertensive emergency and hypertensive crisis could not be ruled out as the events occurred on the same day or within a day of the most recent dose of donanemab. A likely contributory factor in this case was underlying hypertension, as the patient had uncontrolled blood pressure prior to the infusion (173/94 mmHg). Concomitant medication use with Thomapyrin and ibuprofen were potentially contributory to the events of hypertension.

The sponsor noted that for the blinded safety population, 6% of participants discontinued treatment due to an adverse event at the time of the 90-Day Safety Update.³⁶ The most frequently reported reasons for discontinuation included infusion related reaction (1.3%) and ARIA-E (1.0%).

³⁵ Additional details of the narrative are noted in the sponsor's response dated September 7, 2022, to an information request dated September 6, 2022.

³⁶ Noted on page 60 of the Safety Update Report, submitted August 17, 2022.

Narratives for Study Withdrawal

A review of the narratives of cases of ARIA-E, ARIA-H, cerebral microhemorrhage, and superficial siderosis of the central nervous system reported to lead to study withdrawal indicated that the withdrawals were driven by protocol.

One case of suicidal ideation was reported to lead to study withdrawal in one participant (15T-MC-AACG- (b) (6)). The AE occurred 107 days after the first dose of donanemab and 46 days after the third dose. Twenty-six days prior to the event of suicidal ideation, the patient reported the AE of Covid-19 (duration of 22 days). A role for donanemab in this case could not be ruled out given that the participant was exposed to donanemab; however, the participant had history of depression as a risk factor. In addition, the recent infection with Covid-19 may have played a role in the event of suicidal ideation, as Covid-19 infection has been associated with worsening of mood disorders.^{37,38}

One case of hypersensitivity was reported to lead to treatment discontinuation and study withdrawal (15T-MC-AACI- (b) (6)). Twenty cases of infusion related reaction were reported to lead to study withdrawal, which was in part driven by protocol.³⁹ One of the cases of infusion related reaction reported an increase in blood pressure to 240/120 mmHg. The case is summarized here.

Infusion related reaction, I5T-MC-AACI- (b) (6)

64-year-old female with past medical history of AD, depression, hyperlipidemia, gastresophageal reflux disease, irritable bowel syndrome, and migraine, who experienced the AE of severe infusion related reaction 58 days after the first dose of donanemab and on the same day as the third dose of donanemab. The patient's blood pressure prior to the third infusion was 120/70 mmHg with a pulse rate of 67 beats per minute. On the same day, the participant experienced infusion related reaction, characterized by trouble breathing, tachypnea, hypertensive to 240/120 mmHg, tachycardia to 130 beats per minutes, irregular heart rate, chest pain, and back pain. The infusion was stopped four minutes after starting

³⁷ Alonso-Lana S, Marquie M, Ruiz A, et al. Cognitive and neuropsychiatric manifestations of Covid-19 and effects on elderly individuals with dementia. *Frontiers in Aging Neuroscience* 2020; 12: 1-15.

³⁸ Taquet M, Sillett R, Zhu L, et al. Neurological and psychiatric risk trajectories after SARS-CoV-2 infection: an analysis of 2-year retrospective cohort studies including 1 284 437 patients. *Lancet Psychiatry* 2022. doi: 10.1016/S2215-0366(22)00260-7.

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because of the infusion related reaction. No treatment was reported, and the reaction was reported to resolve the following day. Concomitant medications included dicycloverine, escitalopram, and pantoprazole. The study drug was withdrawn because of the AE of infusion related reaction.

Reviewer comment: A role for donanemab in the AE of infusion related reaction is likely given onset during infusion. The case is notable for the elevated blood pressure and elevated heart rate that were recorded that time of the infusion related reaction.

One case of SAE of drug eruption reported to lead to treatment discontinuation and study withdrawal is discussed in the Narratives section of the Serious Adverse Events section of this review ([I5T-MC-AACG-](#)(b) (6)).

Three cases of anaphylactic reaction reported to lead to treatment discontinuation and study withdrawal are discussed in the Narratives section of the Serious Adverse Events section of this review ([I5T-MC-AACI-](#)(b) (6), [I5T-MC-AACI-](#)(b) (6) and [I5T-MC-AACI-](#)(b) (6)).

Narratives for Treatment Discontinuations

The reviewer notes two cases of infusion related reaction associated with collapse/fainting (I5T-MC-AACI-(b) (6) and I5T-MC-AACI-(b) (6)). The cases are summarized here.

Infusion related reaction, [I5T-MC-AACI-](#)(b) (6)

An 83-year-old female with past medical history of AD, hypertension, hyperlipidemia, who experienced adverse events of infusion related reaction 57 days (day of the 3rd infusion) and 85 days (day of the fourth infusion) after starting treatment with donanemab. Concomitant medications included losartan, escitalopram, and amlodipine. On Study Day 57, prior to the infusion, the blood pressure was 139/71 mmHg and pulse rate was 60 beats/min. The patient experienced the AE of moderate infusion related reaction. The infusion was given over 30 minutes. The patient experienced symptoms of headache, chills, bradycardia (heart rate not reported), and collapse/fainting within 30 minutes of the end of study drug administration.⁴⁰ No treatment was reported, and the AE was reported as resolved on the same day.

On Study Day 85, the dose was increased to 1400 mg. The patient's blood pressure was 125/69 mmHg and pulse rate was 67 beats/min. The patient experienced a moderate infusion related reaction, and the infusion was stopped within 15 minutes of starting because of the AE of infusion related reaction.

⁴⁰ No additional vital signs available as noted by the sponsor in a response dated 9.15.22 to an information request dated 9.13.22.

The patient experienced symptoms of chest pain, low blood pressure (value not reported), fear/panic, abdominal pain, nausea/vomiting, chills, feeling hot, and collapse/fainting. No treatment was reported for the AE of infusion related reaction and the AE was reported as resolved on the same day. The study drug was withdrawn due to the AE of infusion related reaction.

Reviewer comment: A role for donanemab in the events of infusion related reactions is likely given onset during the infusion. The case is notable for symptoms of syncope and collapse associated with the infusion related reaction.

Infusion related reaction, I5T-MC-AACI- (b) (6)

A 75-year-old female with hypercholesterolemia on atorvastatin who experienced a severe infusion related reaction on the same day as the fourth dose of donanemab (Study Day 78). Preinfusion, her blood pressure was 140/70 mmHg and pulse rate was 66 beats per minute. The study drug was stopped 10 minutes into the infusion. During the drug administration, she had experienced chills, malaise, nausea/vomiting, low blood pressure (value not reported), irregular heart rate, vertigo, and collapse/fainting.⁴¹ The study drug was withdrawn as a result of the infusion related reaction. The infusion related reaction resolved the same day.

Reviewer comment: A role for donanemab in the event of infusion related reaction is likely given occurrence at the time of infusion.

The reviewer notes one of infusion related reaction that also reported increases in blood pressure and led to treatment discontinuation. The case is summarized here.

Infusion related reaction, I5T-MC-AACI- (b) (6)

76-year-old female with past medical history of diabetes mellitus type 2, coronary artery bypass, who experienced the AE of moderate infusion related reaction on the day of her second dose of donanemab (Study Day 29). Preinfusion, the blood pressure was 142/76 mmHg and pulse rate was 75 beats/min. During drug administration, the patient experienced symptoms of elevated blood pressure (value not reported), palpitations, nausea/vomiting, erythema on face and neck, chills, rigor, and difficulty breathing/dyspnea.⁴² The patient received treatment with methylprednisolone and diphenhydramine and the AE was reported as resolved on the same day as onset. The infusion was interrupted and then completed on that day. On the day of her third dose (Study Day 62), the patient was administered with diphenhydramine and

⁴¹ No additional vital signs available as noted by the sponsor in a response dated 9.15.22 to an information request dated 9.13.22

⁴² No additional vital signs available as noted by the sponsor in a response dated 9.15.22 to an information request dated 9.13.22

paracetamol for prophylaxis. The infusion was given over 60 minutes. The patient experienced a moderate infusion related reaction, characterized by elevated blood pressure, nausea/vomiting, chills, and myalgia within 30 minutes of end of study drug administration. The patient received treatment with methylprednisolone and diphenhydramine and the AE was reported as resolved on the same day of its onset. The study drug was permanently discontinued due to the AE of infusion related reaction.

Reviewer comment: A role for donanemab in the events of infusion related reaction is likely given onset during the donanemab infusions. The case is notable for repeat infusion related reaction despite the administration of medications prophylactically for infusion related reaction and despite the study drug being administer over 60 minutes (minimum time for infusion to be given was 30 minutes by protocol).

A role for donanemab in the cases of infusion related reaction was likely given temporal association with donanemab infusions.⁴³ All of the AEs occurred within 24 hours of the infusion, except for the case of urticaria, which occurred 7 days after the most recent infusion (I5T-MC-AACG-(b) (6)).

A review of the narratives of cases of ARIA-E, ARIA-H, cerebral microhemorrhage, and superficial siderosis of the central nervous system reported to lead to treatment discontinuation indicated that most discontinuations were driven by protocol.

A role for donanemab in one case of humerus fracture reported to lead to treatment discontinuation could not be established as the participant had risk factors for fracture, including postmenopausal state and history of previous fracture (I5T-MC-AACI-(b) (6)).

8.4.4. Significant Adverse Events

⁴³ Chills/I5T-MC-AACG-(b) (6) Flushing/I5T-MC-AACG-(b) (6) Urticaria/I5T-MC-AACG-(b) (6)
Nausea/I5T-MC-AACG-(b) (6) infusion related reaction/I5T-MC-AACG-(b) (6) I5T-MC-AACG-(b) (6)
I5T-MC-AACI-(b) (6) I5T-MC-AACI-(b) (6) I5T-MC-AACI-(b) (6) I5T-MC-AACI-(b) (6) I5T-MC-
AACI-(b) (6) I5T-MC-AACI-(b) (6) I5T-MC-AACI-(b) (6) I5T-MC-AACI-(b) (6) I5T-MC-AACI-(b) (6)
(b) (6) I5T-MC-AACI-(b) (6) and I5T-MC-AACI-(b) (6)

Definitions for mild, moderate, and severe categories for severity of AEs were not included in the protocol for Study AACG. In a response dated August 12, 2022, to an information request dated August 10, 2022, the sponsor notes that mild, moderate, and severe categorization of intensity of AEs were conducted according to the principal investigator judgement. The reviewer notes that the lack of definitions for AE severity classification can result in inconsistent categorization of AE severity among principal investigators.

Definitions for mild, moderate, and severe categories for intensity of AEs were included in the protocols of the open-label studies.

A similar frequency of severe TEAEs was observed in donanemab and placebo arms of Study AACG. ARIA-E and infection were the most frequently reported severe TEAEs in Study AACG. ARIA-E, allergic reaction/hypersensitivity, and infection were the most frequently reported severe TEAEs in the all-donanemab pool at the time of the 90-Day Safety Update.

A similar frequency of participants experiencing a severe TEAE was observed in both donanemab and placebo arms (16% versus 14%, respectively). The following table shows TEAEs by severity category in Study AACG.

Table 19. Frequency of a Participant Experiencing at Least One TEAE by Severity Categories in Study AACG

Adverse Event Severity	DON N=131 n (%)	Placebo N=125 n (%)
Mild	106 (81)	97 (78)
Moderate	77 (59)	64 (51)
Severe	21 (16)	17 (14)

The reviewer created this using the IDB ADAE dataset submitted 8.25.22, SAFFL = Yes, StudyID=AACG, PCIN57FL = Yes, TRTEMFL = Yes, AESEV= mild, moderate, or severe.

ARIA-E and infection were among the most frequent observed severe TEAEs in Study AACG. One AE of sinus node dysfunction was reported in one subject and is discussed in the Narratives section of the Serious Adverse Events section of this review (I5T-MC-AACG-^{(b) (6)}). One AE of sinus arrest (verbatim term: short sinus pause) was reported in one subject (I5T-MC-AACG-^{(b) (6)}). In this case, a role for donanemab in the event could not be established as the participant had additional risk factors for the development of this AE including history of tobacco use, hypertension, and hyperlipidemia. One case of small intestinal obstruction was reported 16 days after the fourth dose of the drug and 106 days since the first dose of the drug (I5T-MC-AACG-^{(b) (6)}). In this case, the participant also experienced the AEs of benign prostatic hyperplasia, urinary retention, bilateral hydronephrosis, acute kidney injury, hypocalcemia, nausea, vomiting, and malnutrition on the same day. A role for donanemab

could not be established given the concurrent events. The following table shows severe TEAEs in Study AACG by preferred and grouped terms with frequency of at least 2% higher in the donanemab arm compared to placebo.

Table 20. Severe TEAEs by Preferred and Grouped Terms with Frequency of at Least 2% Higher in the Donanemab Arm Compared to Placebo in Study AACG

Adverse Event Severity	DON N=131 n (%)	Placebo N=125 n (%)
ARIA-E ¹	7 (5)	0
Infection MQG	5 (4)	1 (1)
Pneumonia	3 (2)	0
Bacterial Sepsis	1 (1)	0
Clostridium Difficile Colitis	1 (1)	0
Staphylococcal Infection	0	1 (1)
ARIA-H Microhemorrhage ¹	2 (2)	0
Infusion Related Reaction	2 (2)	0
Sinus Node Arrest, Pause, Block, Dysfunction MQG	2 (2)	0
Sinus Arrest	1 (1)	0
Sinus Node Dysfunction	1 (1)	0
Diarrhea, Colitis, Enteritis, Proctitis MQG	2 (2)	0
Clostridium Difficile Colitis	1 (1)	0
Diarrhea	1 (1)	0
Malignancy Fda N MQG	2 (2)	0
Breast Cancer	1 (1)	0
Lung Adenocarcinoma	1 (1)	0
Stage II Non-Small Cell Lung Cancer	1 (1)	0
Vomiting Fda B MQG	2 (2)	0
Small Intestinal Obstruction	1 (1)	0
Vomiting	1 (1)	0

¹Assessment of severity of ARIA is based on the clinician's assessment of severity of ARIA events noted in the adverse events dataset. For a radiographic assessment of events of ARIA, the reader is referred to the section on [ARIA](#) in this review. MQG: MedDRA Query Group. The reviewer created this using the IDB ADAE dataset submitted 8.25.22, SAFFL = Yes, StudyID=AACG, PCIN57FL = Yes, TRTEMFL = yes, AESEV= severe.

At the time of the 90-Day Safety Update, 6% (78/1304) of participants in the all-donanemab pool reported experiencing at least one severe TEAE. ARIA-E, allergic reaction/hypersensitivity, and infection were among the most frequently reported TEAEs leading to treatment discontinuation. The cases of anaphylactic reaction and bacterial sepsis are discussed in the Narratives section of the Serious Adverse Events section of this review ([I5T-MC-AACI-](#) (b) (6))

and [I5T-MC-AACG-](#) (b) (6) respectively). The following table shows severe TEAEs by preferred term and groups of preferred terms with frequency of at least 1% in the all-donanemab group after the 90-Day Safety Update.

Table 21. Severe TEAEs by Preferred and Grouped Terms with Frequency of at Least 1% in the All-Donanemab Group after the 90-Day Safety Update

Adverse Event	DON N=1304 n (%)
ARIA-E ¹	20 (2)
Allergic Reaction and Hypersensitivity MQG	10 (1)
Infusion Related Reaction	8 (1)
Anaphylactic Reaction	1 (<0.5)
Hypersensitivity	1 (<0.5)
Infection MQG	7 (1)
Pneumonia	3 (<0.5)
Bacterial Arthritis	1 (<0.5)
Bacterial Sepsis	1 (<0.5)
Clostridium Difficile Colitis	1 (<0.5)
Peritonitis	1 (<0.5)

¹Assessment of severity of ARIA is based on the clinician's assessment of severity of ARIA events noted in the adverse events dataset. For a radiographic assessment of events of ARIA, the reader is referred to the section on [ARIA](#) in this review. MQG: MedDRA Query Group. The reviewer created this using the IDB ADAE dataset submitted 8.25.22, SAFFL = Yes, TRT01A = inversion of Dona-C, SAFFL = Yes, LYIN57FL = Yes, TRTEMFL = yes, AESEV=mild.

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

The most frequently reported TEAEs in Study AACG were ARIA-E, ARIA-H Microhemorrhage, ARIA-H Superficial Siderosis, nausea/vomiting, and infusion related reaction. ARIA-E was reported in up to 27% of donanemab-treated participants versus 1% on placebo. ARIA-H microhemorrhage occurred in up to 20% of donanemab-treated participants compared to 5% on placebo. ARIA-H Superficial Siderosis occurred in up to 17% of donanemab-treated participants compared to 2% on placebo. Nausea/vomiting occurred in up to 13% of donanemab-treated participants compared to 5% on placebo. Infusion related reaction occurred in up to 8% of donanemab-treated participants compared to none on placebo. TEAEs occurring in less than 5% of donanemab-treated participants and at least 2% more than placebo in Study AACG included bronchitis/lower respiratory tract infection, hypotension, and bradycardia. In the all-donanemab-treated pool, ARIA-E, ARIA-H-Microhemorrhages, and headache were among the most frequently reported TEAEs.

In the key safety studies, ARIA events were recorded as adverse events and as MRI findings. ARIA-E findings were required to be reported as adverse events by investigators, but this was not specified for ARIA-H events. This reviewer considered the dataset containing MRI findings to be the more comprehensive dataset for ARIA findings and as a result, analyses related to ARIA in the common AEs table for labeling use frequencies obtained from analyzing the MRI dataset.

In Study AACG, the frequency of participants reporting at least one TEAE in the donanemab arm and placebo arms in the adverse event dataset was the same (90%, 118/131 and 112/125, respectively).

ARIA-E, ARIA-H Microhemorrhage, ARIA-H Superficial Siderosis, nausea and vomiting, and infusion related reactions were among the most frequently reported TEAEs in Study AACG. The following table shows this reviewer's recommendations for grouping of preferred terms in Study AACG (b) (4). A cut off frequency of at least 5% and at least 2% higher in the donanemab arm compared to placebo was used in the common AEs table (b) (4).

Table 22. TEAEs with Frequency of at least 5% and at least 2% higher in the Donanemab Arm Compared to Placebo (b) (4) in Study AACG

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

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

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

(b) (4)

Table 23. TEAEs with Frequency of at least 2% and at least 2% higher in the Donanemab Arm Compared to Placebo in Study AACG (b) (4)

Adverse Event	DON N=131 n (%)	Placebo N=125 n (%)
Bronchitis, Bronchiolitis, Tracheitis, Alveolitis, Bronchiectasis MQG	6 (4.6)	2 (1.6)
Bronchitis	4 (3.1)	2 (1.6)
Viral Bronchitis	1 (0.8)	0
Lower Respiratory Tract Infection	1 (0.8)	0
Hypotension Fda N MQG	6 (4.6)	3 (2.4)
Orthostatic Hypotension	2 (1.5)	0
Hypotension	4 (3.1)	3 (2.4)
Bradycardia ¹	3 (2.3)	0
Sinus Bradycardia	2 (1.5)	0
Bradycardia	1 (0.8)	0

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

¹Grouped term

The reader is referred to the [Vital Signs section](#) and the [ECG section](#) of this review for analyses related to bradycardia. One SAE of bradycardia was reported in one subject in Phase 2 and 3 Studies (IST-MC-AACI- (b) (6)). In this case, the reviewer did not identify a role for donanemab in the event as the participant went on to receive three additional doses of donanemab without experiencing the event. The case is discussed further in the [Serious Adverse Events section](#) of this review.

Hypotension/orthostatic hypotension were reported with higher frequency in the donanemab arm compared to placebo (5% versus 2%, respectively). No serious cases with preferred term of Hypotension or Orthostatic Hypotension were identified in Phase 2 and 3 Studies. A higher frequency of donanemab-treated participants experienced orthostatic changes in diastolic blood pressure compared to placebo in Study AACG. The reader is referred to the [Vital Signs section](#) of this review for further details.

The reviewer is referred to the [Appendix](#) for most common TEAEs occurring in Study AACG by preferred term and by grouped terms using the adverse event dataset and for most common TEAEs occurring in Study AACG within the first twelve weeks of treatment.

At the time of the 90-Day Safety Update, TEAEs were reported in 69% (903/1304) of participants in the all-donanemab-treated group in the adverse event dataset.

ARIA-E, ARIA-H microhemorrhages, and headache were among the most frequently reported TEAEs by preferred term. The following table shows TEAEs by preferred term in the all-donanemab pool at the time of the 90-Day Safety Update.

Table 24. TEAEs by Preferred Term with Frequency of at Least 5% in the All-Donanemab Pool in the 90-Day Safety Update.

Adverse Event	DON N=1304 n (%)
ARIA-E ¹	229 (18)
ARIA-H Microhemorrhage ¹	203 (16)
Headache	124 (10)
Infusion Related Reaction	115 (9)
ARIA-H Superficial Siderosis ¹	105 (8)
Covid-19	70 (5)
Fall	69 (5)

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

The reviewer created this using the 90-Day Safety IDB ADAE dataset submitted 8.25.22, TRT01A = inversion of Dona-C, SAFFL = Yes, LYIN57FL = Yes, TRTEMFL = Yes.

Grouped terms related to infection, headache, and allergic reaction/hypersensitivity were reported with frequency of at least 10% or higher in the all-donanemab pool at the time of the 90-Day Safety Update. The following tables show TEAEs by ODE-1 grouped terms and by FDA Narrow grouped terms with frequency of at least 5% in the all donanemab-pool in the 90-Day Safety Update. The reader is referred to Section 13.1 of the Appendix for the preferred terms that contributed to the grouped terms.

Table 25. TEAEs by ODE-1 Grouped Terms with Frequency of at Least 5% in the All-Donanemab Pool in the 90-Day Safety Update.

Adverse Event	DON N=1304 n (%)
Infection MQG	197 (15)
Headache MQG	136 (10)
Allergic Reaction and Hypersensitivity MQG	132 (10)
Fall, Dizziness, Balance Disorder MQG	118 (9)
Upper Respiratory Infection, Cold, Rhinitis, Upper Respiratory Tract Infection MQG	71 (5)

MQG: MedDRA Query Group. The reviewer created this using the 90-Day Safety IDB ADAE dataset submitted 8.25.22, TRT01A = inversion of Dona-C, SAFFL = Yes, LYIN57FL = Yes, TRTEMFL = Yes.

Table 26. TEAEs by FDA Narrow Grouped Terms with Frequency of at Least 5% in the All-Donanemab Pool in the 90-Day Safety Update.

Adverse Event	DON N=1304 n (%)
Headache Fda N MQG	138 (11)
Local Administration Reactions Fda N MQG	121 (9)
Hemorrhage Fda N MQG	74 (6)
Dizziness Fda N MQG	66 (5)

MQG: MedDRA Query Group. The reviewer created this using the 90-Day Safety IDB ADAE dataset submitted 8.25.22, TRT01A = inversion of Dona-C, SAFFL = Yes, LYIN57FL = Yes, TRTEMFL = Yes.

8.4.6. Laboratory Findings

The reviewer did not identify any clinically meaningful changes in laboratory values in a review of the sponsor's analyses of mean change from baseline, shifts to high values, low values, and CTCAE toxicity Grades 3 through 5 for laboratory values related to chemistry or hematology. Additionally, this reviewer did not identify any clinically meaningful changes in a review of mean change from baseline and shift to abnormal for urine studies. TEAEs related to laboratory findings were reported with similar frequency in donanemab and placebo arms in Study AACG. A similar frequency of participants in the donanemab and placebo arms of Study AACG had increases in AST and ALT, alkaline phosphatase, and bilirubin in Study AACG (difference no > 1%). No donanemab-treated participants met Hy's Law.

Data in this section is noted in the sponsor's responses dated August 19, 2022, to an information request dated August 9, 2022, the sponsor's response dated September 12, 2022, to an information request dated September 1, 2022, and from the reviewer's own analyses.

For analyses related to laboratory findings, the sponsor evaluated mean change from baseline, shift to high and low lab values, and shift analyses for labs with CTCAE toxicity grades > 3, 4, or 5. Lab tests included blood hematology, chemistry, and urine analyses.⁴⁴ As noted previously in the Routine Clinical Tests section of this review, Study AACN-Dona cohort did not contribute to findings related to laboratory values, as no participants had reached the timepoint of post-baseline laboratory testing (Week 24).

⁴⁴ These analyses were noted in responses dated August 19, 2022, to an information request dated August 9, 2022, and for the 90-Day Safety Update, in a response dated September 12, 2022, to an information request dated September 1, 2022.

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Overall, this reviewer found the sponsor's analyses of laboratory findings to be acceptable, except for an absence of shift analyses for urine studies. This reviewer conducted her own analyses for these studies.

In a review of the sponsor's analyses of mean change from baseline, this reviewer did not identify any clinically meaningful changes with laboratory findings, because of small magnitudes of difference from baseline values in Study AACG and the all-donanemab pool.

This reviewer did not identify any clinically meaningful differences between placebo and donanemab arms in a review of the sponsor's analyses of shift to high and low lab values and shift analyses with CTCAE toxicity grade > 3, 4, or 5 for Study AACG, because of similar frequencies in shifts between placebo and donanemab arms.

A higher frequency of donanemab-treated participants compared to placebo-treated had shift to low lymphocyte counts in Study AACG; however, the clinical significance of this is unknown, given the small magnitude of difference in mean values between donanemab and placebo arms. In Study AACG, a higher frequency of donanemab-treated participants compared to placebo-treated had shift from normal to low for lymphocyte with CTCAE Grade 1 toxicity (16.8% versus 9.6%, respectively).⁴⁵ Mean change from baseline for lymphocyte showed statistically significant lower values in the donanemab arm compared to placebo (p values < 0.05) at Weeks 12, 24, and 36; however, mean differences were small (no greater than $0.10 \times 10^9/L$, normal reference range for lymphocytes of $0.8 - 3.0 \times 10^9/L$). The maximal minimum value for lymphocyte count in Study AACG was $0.41 \times 10^9/L$ (occurring at Week 24). By Week 76, the mean difference in change from baseline between placebo and donanemab arms had decreased to $0.05 \times 10^9/L$. In the all-donanemab pool, 10.1% of donanemab-treated subjects with normal baseline for lymphocytes had shift to CTCAE Grade 1 for decreased lymphocytes.⁴⁶ The maximal minimum value for the all-donanemab pool for lymphocyte count among Week 12, 24, and 36 visits was $0.29 \times 10^9/L$ (occurring at Week 12).

The reviewer notes two subjects with CTCAE Grade 4 creatine phosphokinase increases; however, in both cases a role for donanemab was unlikely as CPK levels decreased despite additional doses of donanemab (I5T-MC-AACG-(b) (6) 4680 U/L and I5T-MC-AACI-(b) (6) 4113 U/L).⁴⁷

⁴⁵ Noted on page 531 of the sponsor's response dated August 19, 2022, to an information request dated August 9, 2022.

⁴⁶ Noted on page 205 of the sponsor's response dated September 12, 2022, to an information request dated September 1, 2022.

⁴⁷ Noted starting on page 6 of the sponsor's response dated October 24, 2022, to an information request dated October 21, 2022.

A review of the sponsor's analyses for mean change from baseline for urine analyses related to pH and specific gravity in Study AACG did not identify any clinically meaningful changes, because of small magnitudes of change in mean values observed. This reviewer evaluated shift to abnormal values for urine studies and did not identify an imbalance between the donanemab and placebo arms in Study AACG.

TEAEs related to laboratory findings

In Study AACG, subjects in the donanemab and placebo arms reported similar frequencies of TEAEs related to laboratory findings and belonging to the SOC of Investigations (difference no greater than 1%). No TEAEs were serious or lead to treatment discontinuation or study withdrawal.

In the all-donanemab pool at the time of the 90-Day Safety Update, no TEAEs related to laboratory findings and belonging to the SOC of Investigations were reported with frequency of at least 1%. No TEAEs were serious or lead to treatment discontinuation or study withdrawal.

Acute kidney injury

In Study AACG, the donanemab and placebo arms had the same frequency of participants reporting the TEAE of acute kidney injury (2%, 2/131 and 2/125, respectively).

In the all-donanemab pool, acute kidney injury was reported in 6 participants (6/1304, 0%). In five of the six participants, the acute kidney injury occurred within 57 days of treatment with donanemab. One of the five events was an SAE (I5T-MC-AACI- (b) (6)). In three of the five events, a role for donanemab in the events could not be established because of concurrent events that were likely contributory (pneumothorax and rib fractures/I5T-MC-AACI- (b) (6) severe small intestinal obstruction/I5T-MC-AACG- (b) (6) and Covid-19 infection/I5T-MC-AACI- (b) (6)). In the fourth event, a role could not be established as the lab was drawn prior to the first infusion of donanemab (I5T-MC-AACI- (b) (6)). In the remaining case, a role could not be established because of negative rechallenge (I5T-MC-AACI- (b) (6)). The event occurred 22 days after the 3rd dose and the patient went on to have three more doses without reoccurrence. None of the TEAEs of acute kidney injury led to treatment discontinuation or study withdrawal.

Hepatic-Related Events

A similar frequency of subjects in the donanemab and placebo arms had increases in AST and ALT, alkaline phosphatase, and bilirubin in Study AACG (difference no > 1%). The following table shows shift analyses submitted by the sponsor for hepatic-related lab findings in Study AACG.

Table 27. Maximum Post-Baseline Values For Liver Enzymes in Study AACG

Lab Test	Cut Point	DON	Placebo

		N=131	N=125
ALT	≥3*ULN	1/131 (0.8)	0/124 (0)
	≥5*ULN	0/131 (0)	0/124 (0)
	≥10*ULN	0/131 (0)	0/124 (0)
AST	≥3*ULN	0/131 (0)	0/124 (0)
	≥5*ULN	0/131 (0)	0/124 (0)
	≥10*ULN	0/131 (0)	0/124 (0)
ALP	≥2*ULN	0/131 (0)	1/124 (0.8)
BILI	≥2*ULN	0/131 (0)	0/124 (0)

Data from this table was taken from the sponsor's analyses noted in Table APP.11 (page 484) of the sponsor's response dated August 19, 2022, to an information request dated August 9, 2022. Baseline category includes participants with normal and abnormal values for liver enzymes.

In the all-donanemab pool, one additional participant met maximum post-baseline cut point values for liver enzymes noted in the table above (2/1196 [0.2%] with alkaline phosphatase ≥2*ULN).

The donanemab had placebo arms had similar frequency of TEAEs belonging to the broad and narrow SMQs of Hepatic disorders (Levels 1 through 4) and Biliary disorders (Levels 1 through 4) in Study AACC.

No TEAEs of acute hepatitis failure, drug-induced liver injury, hepatic failure, hepatic necrosis, or fulminant hepatitis were reported in Study AACC, AACD, Study AACG or the all-donanemab pool.

This reviewer reviewed the lab datasets for Studies AACC, AACD, and the all-donanemab pool and no donanemab-treated participants met Hy's law.

8.4.7. Vital Signs

Higher frequencies of bradycardia, orthostatic changes in diastolic blood pressure, and TEAEs related to bradycardia and hypotension were observed in donanemab-treated participants in Study AACC. Increases and decreases in blood pressure and increases in heart rate were identified in participants experiencing infusion related reactions and are discussed in the [Hypersensitivity and Infusion Related Reactions](#) section of this review. A review of mean change from baseline for vital signs, shift analyses for vital signs other than pulse rate and orthostatic diastolic blood pressure, and TEAEs related to vital signs and belonging to the SOC of Investigations did not identify a safety signal related to vital signs.

Data in this section is noted in the sponsor's responses dated August 19, 2022, to an information request dated August 9, 2022, the sponsor's response dated September 12, 2022, to an information request dated September 1, 2022, and from this reviewer's own analyses.

The sponsor evaluated mean change from baseline and shift from normal to potentially clinically significant high and low vital signs for blood pressure, pulse, orthostatic change in blood pressure and pulse, temperature, and weight in Studies AACG, AACH, and AACI. Study AACN-Dona cohort did not contribute to vital sign analyses, as vital signs were not collected by case report form.⁴⁸

Overall, this reviewer found the sponsor's analyses to be acceptable.

This reviewer did not identify any clinically meaningful changes in the sponsor's analyses of mean change from baseline for vital signs, because of small magnitudes of difference from baseline values in Study AACG and the all-donanemab pool.

Shift in Heart Rate to Less than 60 Beats Per Minute

A higher frequency of donanemab-treated participants had shift in heart rate from normal to < 60 beats per minute overall in Study AACG (32% versus 29%, respectively). A review of minimum mean baseline pulse rate showed similar values in donanemab and placebo arms (60.2 beats per minute versus 60.6 beats per minute, respectively).⁴⁹ The following table shows the frequency of participants with shift in pulse rate from normal to less than 60 beats per minute in Study AACG.

Table 28. Frequency of Participants with Shifts in Pulse Rate from Normal to < 60 beats per minute in Study AACG

Time	Donanemab N=131 n (%)	Placebo N=125 n (%)
Any Visit ¹	31/97 (32)	29/100 (29)
Week 4	13/79 (16)	16/87 (18)
Week 8	10/77 (13)	16/84 (19)
Week 12	10/74 (14)	11/80 (14)
Week 16	9/71 (13)	9/78 (12)
Week 20	13/71 (18)	6/77 (8)
Week 24	15/66 (23)	15/76 (20)
Week 28	9/64 (14)	8/76 (11)
Week 32	6/61 (10)	9/75 (12)

⁴⁸ Noted by the sponsor in a response dated June 22, 2022, to information requests dated June 21, 2022, and June 22, 2022.

⁴⁹ Noted in Table APP.2.7.4.7.12 on page 289 of the Clinical Summary of Safety Appendix

Time	Donanemab N=131 n (%)	Placebo N=125 n (%)
Week 36	5/56 (9)	12/71 (17)
Week 40	6/53 (11)	6/69 (9)
Week 44	5/49 (10)	7/64 (11)
Week 48	6/53 (11)	6/63 (10)
Week 52	9/49 (18)	10/60 (17)
Week 56	10/49 (20)	4/55 (7)
Week 60	5 /47(11)	5/57 (9)
Week 64	13/51 (25)	13/56 (23)
Week 68	7/53 (13)	8/58 (14)
Week 72	7/53 (13)	9/61 (15)
Week 76	13/54 (24)	12/64 (19)

¹Data for shift in pulse rate from normal to < 60 beats/minute at any visit taken from page 125 of the sponsor's response dated 8.19.22 to an information request dated 8.9.22. For Week 4 through 76, the reviewer created this table using the IDB 90 Day Safety Update ADVS, StudyID = AACG, TRTA = Placebo or Dona-M, AVISIT = Weeks 4 through 76, parameter = sitting pulse, BASECAT1 = high/normal, AVALCAT1 = Low.

Similar findings on ECG analyses of higher frequencies of shift to lower heart rate were observed in the donanemab arm in Study AACG. The reader is referred to the [ECG section](#) of this review for these findings.

A higher frequency of TEAEs of sinus bradycardia and bradycardia were reported in the donanemab arm compared to placebo in Study AACG (2% [3/131] versus none, respectively).

One SAE of bradycardia was reported in one subject in Phase 2 and 3 Studies (I5T-MC-AACI-^{(b) (6)}). In this case, the reviewer did not identify a role for donanemab in the event as the participant went on to receive three additional doses of donanemab without experiencing the event. The case is discussed further in the [Serious Adverse Events section](#) of this review.

Orthostatic Change in Diastolic Blood Pressure

A higher frequency of donanemab-treated participants compared to placebo had orthostatic changes in diastolic blood pressure at visits where orthostatic vital signs were measured in Study AACG. At baseline, donanemab and placebo arms had similar mean maximum orthostatic changes in diastolic blood pressure (3 mmHg versus 2.6 mmHg respectively).⁵⁰ The following table shows the frequency of participants with orthostatic change in diastolic blood pressure in Study AACG.

⁵⁰ Noted in Table APP.2.7.4.7.12 on page 290 of the Clinical Summary of Safety Appendix.

Table 29. Frequency of Participants with Orthostatic Change in Diastolic Blood Pressure in Study AACG¹

Time	Donanemab N=131 n (%)	Placebo N=125 n (%)
Any Visit	21/118 (17.8)	12/110 (10.9)
Week 12	6/115 (5)	4/108 (4)
Week 24	5/106 (5)	2/104 (2)
Week 36	2/93 (2)	4/97 (4)
Week 52	4/76 (5)	3/83 (4)
Week 64	3/78 (4)	3/79 (4)
Week 76	3/83 (4)	1/88 (1)

¹Orthostatic change in diastolic blood pressure defined as a decrease in blood pressure of 10 mmHg. Data from this table at any visit taken from page 126 of the sponsor's response dated 8.19.22 to an information request dated 8.9.22. For Weeks 12 through 76, the reviewer created this table using the IDB 90 Day Safety Update ADVS, StudyID = AACG, TRTA = Placebo or Dona-M, AVISIT = Weeks 4 through 76, parameter = orthostatic change in DBP, BNRIND = inverse of normal, CRIT2FL = Yes.

A higher frequency of donanemab-treated participants compared to placebo reported TEAEs of orthostatic hypotension in Study AACG (2% versus none, respectively). No serious cases with preferred term of Orthostatic Hypotension were reported in Phase 2 and 3 Studies.

Weight Loss of 7% Or More

The reviewer notes a trend towards a higher frequency of subjects in the donanemab arm compared to placebo with weight loss of 7% or more from baseline across visits in Study AACG; however, the clinical significance of the finding is unknown given the small magnitude of difference in frequencies (no higher than 4% at any of the visits shown in the following table). A review of mean change from baseline for weight showed that by Week 76, the donanemab arm had a similar mean decrease in weight compared to placebo (mean decrease of 0.94 kg versus 0.57 kg, respectively).⁵¹ A review of TEAEs with the preferred term Weight Decreased showed the same frequency observed in donanemab and placebo arms in Study AACG (3%, [4/131 and 4/125, respectively]). The following table shows frequency of subjects with weight loss of 7% or more by visit in Study AACG.

⁵¹ Noted on page 59 of the sponsor's response dated August 19, 2022, to an information request dated August 9, 2022.

Table 30. Frequency of Participants with Weight Loss of 7% or More from Baseline in Study AACG.

Visit	DON N=131	Placebo N=125
Any Visit	18/129 (14.0)	13/120 (10.8)
Week 12	1/125 (1)	0/117 (0)
Week 24	6/114 (5)	2/111 (2)
Week 36	6/101 (6)	6/104 (6)
Week 52	8/85 (9)	5/89 (6)
Week 64	10/88 (11)	7/85 (8)
Week 76	13/92 (14)	9/93 (10)

Data from this table at any visit taken from page 125 of the sponsor's response dated 8.19.22 to an information request dated 8.9.22. For Weeks 12 through 76, the reviewer created this table using the IDB 90 Day Safety Update ADVS, StudyID = AACG, TRTA = Placebo or Dona-M, AVISIT = Weeks 12, 24, 36, 52, 64, and 76, parameter = weight, PCHGCAT1 = Low, grouped on USUBJID and TRT01A.

This reviewer did not identify any clinically significant imbalances between donanemab and placebo arms in shifts to potentially clinically significant high or low values for other vital signs in Study AACG or the all-donanemab pool, because of small magnitudes of difference or because of similar magnitudes of fluctuations between donanemab and placebo arms.

In Study AACG, TEAEs related to vital signs and belonging to the SOC Investigations were balanced between donanemab and placebo arms (difference < 1%).

TEAEs related to vital signs and belonging to the SOC Investigations occurred at a low frequency in the all-donanemab pool (1% or less).

In one donanemab-treated participant who experienced the SAE of hypertensive urgency, the reviewer did not identify a role for donanemab as the onset of the AE occurred at a time that was greater than five times the half-life of the drug (113 days after the last dose of donanemab, I5T-MC-AACI-181-90797).

Increases and decreases in blood pressure were noted in the narratives of some participants at the time of infusion reactions. The reader is referred to the [Hypersensitivity and Infusion-Related Reactions](#) section of this review for further details.

8.4.8. Electrocardiograms (ECGs)

A higher frequency of donanemab-treated participants was observed to have shifts in mean heart rate from normal to < 50 beats per minute and QRS intervals to ≥ 120 msec in Study

AACG. There was no imbalance in participants reporting TEAEs related to ECG changes not related to the QT interval between donanemab and placebo arms in Study AACG.

Data in this section is noted in the sponsor's responses dated August 19, 2022, to an information request dated August 9, 2022, the sponsor's response dated September 12, 2022, to an information request dated September 1, 2022, and from the reviewer's own analyses.

The reader is referred to the Routine Clinical Tests section of this review for methods of ECG collection and ECG reading.

The sponsor analyzed mean change from baseline and shift analyses for mean heart rate, PR interval, QRS interval, and QT interval corrected by Fridericia (QTcF) for evaluation of changes in ECGs associated with donanemab therapy in Studies AACG, AACH, and AACI. Study AACN-Dona cohort did not contribute to ECG analyses, as post-baseline ECGs were not collected.

A review of mean change from baseline for heart rate, PR interval, and QRS interval did not identify any clinically significant changes, because of small magnitudes of difference from baseline values in Study AACG and the all-donanemab pool.

A higher frequency of participants in the donanemab arm compared to placebo had shifts in mean heart rate from normal to less than 50 beats per minute at any visit (17% versus 6.4%, respectively) and across all visits in Study AACG. In the all-donanemab pool at the time of the 90-Day Safety Update, 12.3% (25/203) participants experienced a shift in mean heart rate from normal to < 50 beats per minute at any time.⁵² The following tables shows shifts in mean heart rate from normal to < 50 beats per minute across visits in Study AACG.

Table 31. Frequency of Participants with Shift in Mean Heart Rate from Normal to < 50 beats per Minute in Study AACG

Visit	Donanemab	Placebo
Any Visit	19/112 (17.0)	7/109 (6.4)
Week 24	10/103 (9.7)	1/102 (1.0)
Week 52	3/80 (3.8)	0/83 (0)
Week 64	7/82 (8.5)	2/84 (2.4)
Week 76	5/83 (6.0)	3/85 (3.5)

Data in the table is taken from the sponsor's response dated August 19, 2022, to an information request dated August 9, 2022, page 595.

⁵² Noted on page 231 of the sponsor's response dated September 12, 2022, to an information request dated September 1, 2022.

A higher frequency of participants in the donanemab arm compared to placebo had shifts in QRS intervals from normal to ≥ 120 msec at any time in Study AACG (7.4% versus 3.8%, respectively) and across all visits in Study AACG. In the all-donanemab pool at the time of the 90-Day Safety Update, 5.2% (11/211) of participants experienced a shift in QRS interval from normal to ≥ 120 msec.⁵³ The following tables shows shifts in QRS interval from normal to ≥ 120 msec in Study AACG.

Table 32. Frequency of Participants with Shift in QRS interval from normal to ≥ 120 msec By Visit in Study AACG

Visit	Donanemab	Placebo
Any Visit	9/121 (7.4)	4/106 (3.8)
Week 24	3/107 (2.8)	0/98 (0)
Week 52	5/83 (6.0)	2/81 (2.5)
Week 64	2/85 (2.4)	1/83 (1.2)
Week 76	7/86 (8.1)	2/83 (2.4)

Data in the table is taken from the sponsor's response dated August 19, 2022, to an information request dated August 9, 2022, page 600.

A higher frequency of donanemab-treated participants compared to placebo had mean QTcF shifts from normal to > 450 msec at any time in Study AACG (11.2% versus 8.1%, respectively). The reader is referred to the [QT section](#) of this review for further details on shift analyses related to the QT interval.

Donanemab and placebo arms had similar frequencies of participants with shifts from normal to mean heart rate > 100 beats per minute, PR interval < 120 msec or ≥ 220 msec, and QRS interval < 60 msec in Study AACG (difference $< 3\%$).

Review of TEAEs Related to ECG Changes

A review of TEAEs related to ECG changes and belonging to the SOC of Investigations showed the similar frequencies of participants in donanemab and placebo arms reporting the TEAE of QRS Axis Abnormal in Study AACG (0.76% [1/131] and 0.80% [1/125], respectively).

TEAEs related to ECG changes and belonging to the SOC of Investigations occurred at a low frequency in the all-donanemab pool (1% or less). No TEAE related to ECG changes had frequency of $\geq 1\%$ in the all-donanemab pool. No events were serious or lead to study withdrawal or treatment discontinuation.

⁵³ Noted on page 231 of the sponsor's response dated September 12, 2022, to an information request dated September 1, 2022.

Nine SAEs related to arrhythmias were reported in nine donanemab-treated participants in Phase 2 and 3 Studies. A role for donanemab could not be established in eight of the cases, because of underlying risk factors such as past medical history. In the remaining case with SAE of bradycardia, a role for donanemab could not be established as the participant went on to receive three additional doses of donanemab without experiencing. The reader is referred to the [Narratives](#) section of the Serious Adverse Events section of this review for further details on the cases.

8.4.9. QT

No imbalance was seen with QTcF intervals > 480 msec and > 500 msec between donanemab and placebo arms in Study AACG. A higher frequency of donanemab-treated subjects experienced QTcF intervals > 450 msec compared to placebo (11.2% versus 8.1%, respectively). Given the absence of imbalance with shifts to higher QTcF intervals, the clinical significance of the observed difference in QTcF intervals > 450 msec is unknown. TEAEs of prolonged QT were reported in two (2%) donanemab-treated participants versus none on placebo in Study AACG. No AEs of sudden death, torsades, or ventricular fibrillation were reported in Phase 1 studies, Study AACG, or the all-donanemab pool.

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

Data in this section is noted in the sponsor's responses dated August 19, 2022, to an information request dated August 9, 2022, the sponsor's response dated September 12, 2022, to an information request dated September 1, 2022, and from the reviewer's own analyses.

In the protocol for Study AACG, the sponsor noted in that all analyses of QTc will be carried out using the Fridericia correction (QTcF) method.

A higher frequency of donanemab-treated participants compared to placebo had shifts in QTcF from normal to > 450 msec and reported TEAEs of prolonged QT in Study AACG.

A higher frequency of donanemab-treated participants compared to placebo had mean QTcF shifts from normal to > 450 msec at any time in Study AACG (11.2% versus 8.1%, respectively). No imbalances were noted in mean QTcF shifts from normal to > 480 or > 500 msec between donanemab and placebo arms. The following table shows frequency of subjects with mean QTcF shifts to > 450, >480, and > 500 msec in Study AACG.

Table 33. Frequency of Participants with Shifts from Normal to Elevated QTcF (msec) > 450, 480, and > 500 msec in Study AACG at Any Time.

Mean QTcF interval	Donanemab	Placebo
Mean QTcF > 450 msec	13/116 (11.2)	9/111 (8.1)
Mean QTcF > 480 msec	1/130 (0.8)	1/123 (0.8)
Mean QTcF > 500 msec	0/131 (0)	0/123 (0)

Data in the table is taken from the sponsor's response dated August 19, 2022, to an information request dated August 9, 2022, page 601.

Reviewer comment: Bradycardia and prolonged QRS intervals can potentially confound assessments of QT interval duration and contribute to QT intervals measurement increases. As noted in the section on ECGs, a higher frequency of donanemab-treated participants experienced heart rate of < 50 beats per minute and QRS interval durations of ≥ 120 msec. Although different methods exist to correct QT intervals based on heart rate, these methods may not fully correct for heart rate changes.^{54, 55}

A review of TEAEs related to QT changes and belonging to the SOC of Investigations identified two donanemab-treated participants (1.5% [2/131]) who reported the TEAE of prolonged QT compared to none (0/125) on placebo in Study AACG. No TEAE related to QT changes had frequency of $\geq 1\%$ in the all-donanemab pool. No events were serious or led to study withdrawal or treatment discontinuation.

No AEs of sudden death, torsades, or ventricular fibrillation were reported in Study AACG, AACD, AACG, or the all-donanemab pool.

Prolonged QTcF (QTcF > 450 msec) was not identified in any ECGs in the participant with fatal outcome for the AE with preferred term of death (I5T-MC-AACG- (b) (6)).

In the all-donanemab pool, 8% (17/212) experienced a shift in QTcF from normal to > 450 msec.⁵⁶ The frequency of participants with shifts in QTcF from normal to > 480 msec and > 500 msec in the all-donanemab pool was < 1% (2/231 and 1/233, respectively).

A review of mean change from baseline in QTcF did not identify any clinically significant changes, because of small magnitudes of difference from baseline values in Study AACG and in the all-donanemab pool.

⁵⁴ Khatib R, Sabir F, Omari C, et al. Managing drug-induced QT prolongation in clinical practice. *Postgrad Med J* 2021; 97: 452 – 458.

⁵⁵ Postema P and Wilde A. The Measurement of the QT Interval. *Current Cardiology Review* 2014; 10: 287 – 294.

⁵⁶ Noted on page 237 of the sponsor's response dated September 12, 2022, to an information request dated September 1, 2022.

Narratives

Nine SAEs of syncope were reported in eight donanemab-treated subjects in Phase 2 and 3 studies. A role for donanemab could not be established in seven of the eight cases because of concurrent events, past medical history, or lack of temporal association. In the remaining case, syncope occurred in the setting of a likely infusion related reaction ([I5T-MC-AACI-](#) (b) (6)). The reader is referred to the [Narratives](#) section of the Serious Adverse Events section of this review for further details on SAEs of syncope.

This reviewer did not identify a role for prolonged QT interval in nine SAEs related to the topic of arrhythmia in Phase 2 and 3 Studies. The reader is referred the [Serious Adverse Events](#) section of this review for further details of these cases.

8.4.10. Immunogenicity

In the all-donanemab pool, 84% participants who were evaluable for treatment emergent anti-drug antibody (ADA) responses and had anti-drug antibody data at least 12 weeks since first receiving donanemab had a positive postbaseline treatment emergent ADA status (774/919). All of these participants also had neutralizing antibody present. A higher frequency of participants with higher ADA titers compared to lower ADA titers reported a TEAE of infusion related reactions within 24 hours of a donanemab infusion. The low number of participants in each subgroup of ADA titer (< 50) limits the generalizability of these conclusions.

The immunogenicity of donanemab was evaluated using an anti-drug antibody assay and a neutralizing antibody assay. Among Phase 2 and 3 studies, immunogenicity data was collected in Studies AACG, AACH Part B, and AACI Safety Addendum. In Study AACG, ADA samples were collected preinfusion on Weeks 0, 4, 8, 12, 16, 24, 36, 52, 76, the early discontinuation visit, and if the last scheduled assessment of immunogenicity titer was positive, during the follow up period, which was comprised of visits every 12 weeks until the titer returned to baseline or up to 48 weeks after the last dose of donanemab if the antibody titer had not returned to baseline within 48 weeks of the last dose (Weeks 88 through 124).

In Study AACH Part B, ADA samples were collected on Weeks 0, 4, 8, 16, 24, 36, 48, 60, 72, 84, 96, and the early discontinuation visit.

In Study AACI Safety Addendum, ADA samples were collected on Weeks 0, 4, 8, 12, 16, 24, 36, 52, 76, early discontinuation visit, and Weeks 84 through 120.

Reviewer comment: The Guidance for Industry: Immunogenicity Testing of Therapeutic Protein Products —Developing and Validating Assays for Anti-Drug Antibody Detection (January 2019) recommends obtaining pre-treatment samples, samples at multiple intervals throughout the trial, and samples at approximately five half-lives after last exposure (~60 days given

donanemab's half-life of ~12 days as noted in the sponsor's Clinical Overview). Overall, this reviewer finds the sponsor's sampling strategy to be acceptable.

A participant was treatment-emergent ADA positive if the participant was ADA negative at baseline and had at least one postbaseline status of ADA present with a titer of ≥ 2 times the minimum required dilution of the ADA assay (treatment induced treatment emergent ADA) or if the participant was ADA positive at baseline and had a postbaseline ADA titer 4-fold greater than the baseline titer (treatment boosted treatment emergent ADA).

A neutralizing antibody positive participant was defined as a participant who was treatment emergent ADA positive and had a positive neutralizing antibody for at least one postbaseline ADA sample.

In Study AACG, 92% of donanemab-treated participants had treatment emergent ADA positive status compared to 4% on placebo. All of the participants with treatment emergent ADA positive status had neutralizing antibodies present. The following table shows participants with treatment-emergent donanemab ADA in Study AACG.

Table 34. Participants with Treatment-Emergent Donanemab ADA in Study AACG

Category	DON N=131 n (%)	Placebo N=125 n (%)
Subjects evaluable for TE ADA	129/129 (100)	123/123 (100)
ADA present at Baseline	6 (5)	12 (10)
Neutralizing Abs present at Baseline	1 (1)	7 (6)
Subjects postbaseline TE ADA+	119 (92)	5 (4)
Neutralizing Abs present	119 (92)	5 (4)
Treatment-induced TE ADA+	115 (89)	3 (2)
Treatment-boosted TE ADA+	4 (3)	2 (2)
Subjects postbaseline TE ADA-	10 (8)	118 (96)

TE= treatment-emergent. ADA: anti-drug antibody. Abs: antibodies. The reviewer created this table using ADIS dataset, studyID = AACG, parameter = anti-DON Ab, BASECAT1 = negative or positive ADA.

Because AACH and AACI are ongoing studies, for analyses related to the all-donanemab pool, the sponsor evaluated participants with an ADA assessment at least 12 weeks from the first

donanemab infusion. The sponsor notes that >95% of participants who developed treatment emergent ADA positive status became positive by this time period.⁵⁷

The reviewer found this approach to be acceptable.

In the all-donanemab pool, 84% (774/919) of participants with ADA data at least 12 weeks since first receiving donanemab were treatment emergent ADA positive status, and all of these participants also had neutralizing antibody present. The following table shows ADA data in the all-donanemab pool for participants with ADA data at least 12 weeks since first receiving donanemab.

Table 35. Participants with ADA Data at least 12 Weeks Since First Receiving Donanemab in the All-Donanemab Pool

Category	DON N=939 n (%)
Subjects evaluable for TE ADA	919/919 (100)
ADA present at Baseline	45 (5)
Neutralizing Abs present at Baseline	32 (2)
Subjects postbaseline TE ADA+	774 (84)
Neutralizing Abs present	774 (84)
Treatment-induced TE ADA+	736 (80)
Treatment-boosted TE ADA+	38 (4)
Subjects postbaseline TE ADA-	145 (16)

The reviewer created this table using the IBD ADIS dataset submitted on 10.14.22, TRT = Don-M, SUBJ_GE_12W = TRUE, grouped on USUBJID

The sponsor analysis included evaluating the impact of increasing antibody titers on frequency of TEAEs belonging to the SMQs of Anaphylactic Reaction, Hypersensitivity, and Angioedema, TEAEs with preferred term of infusion related reaction in Study AACG. Because AACH and AACI are ongoing studies, for analyses with participants evaluated by tertile ADA titer levels, the sponsor included participants with ADA assessments of at least 24 weeks from the first donanemab infusion.

⁵⁷ Noted on page 34 of the ISI submitted by the sponsor May 18, 2022.

The reviewer found this approach to be acceptable.

TEAEs belonging to the Hypersensitivity SMQ (narrow) and occurring within 24 hours of a donanemab infusion were reported with higher frequency in donanemab-treated participants with higher ADA titers compared to lower titers in Study AACG (13% versus none, respectively). The following table shows frequency of TEAEs belonging to the SMQs of anaphylactic reaction, hypersensitivity, and angioedema (narrow) by ADA titer tertiles in donanemab-treated participants in Study AACG.

Table 36. Frequency of TEAEs Belonging to the SMQs of Anaphylactic Reaction, Hypersensitivity, and Angioedema (Narrow) by ADA Titer Tertiles in Donanemab-Treated Participants in Study AACG

SMQ, TEAE Onset ¹	Donanemab		
	Lower N=40 n (%)	Middle N=44 n (%)	Upper N=31 n (%)
Anaphylactic reaction, ≤ 24 hours	0	0	0
Anaphylactic reaction, > 24 hours	0	0	0
Hypersensitivity, ≤ 24 hours	0	4 (9)	4 (13)
Hypersensitivity, > 24 hours	1 (3)	1 (2)	3 (10)
Angioedema, ≤ 24 hours	0	0	0
Angioedema, > 24 hours	0	0	1 (3)

¹TEAE onset from the time of the donanemab infusion. The reviewer created this table using the IDB ADAE dataset submitted 8.25.22, SAFFL = Yes, StudyID=AACG, PCIN57FL = Yes, TRTEMFL = yes, SMQ12 through 14NAM, AEDOSEFL = Y or N with IDB ADIS dataset submitted on 10.14.22, selected patients with 24 weeks of data.

As noted in the Infusion-related reactions section of this review, imbalances in the Hypersensitivity SMQ were driven primarily by the preferred term of infusion related reaction. TEAEs with preferred term of infusion related reaction occurred with higher frequency in donanemab-treated participants with higher ADA titers compared to lower titers in Study AACG (13% versus none, respectively). The following table shows frequency of TEAEs with the preferred term of infusion related reaction by ADA titer tertiles in donanemab-treated participants in Study AACG.

Table 37. Frequency of TEAEs with Preferred Term of Infusion Related Reaction by ADA Titer Tertiles in Donanemab-Treated Participants in Study AACG

Onset ¹	Donanemab		
	Lower N=40 n (%)	Middle N=44 n (%)	Upper N=31 n (%)
≤ 24 hours	0	3 (7)	4 (13)
> 24 hours	0	0	1 (3)

¹TEAE onset from the time of the donanemab infusion. The reviewer created this table using the IDB ADAE dataset submitted 8.25.22, SAFFL = Yes, StudyID=AACG, PCIN57FL = Yes, TRTEMFL = yes, AEDECOD= infusion related reaction, AEDOSEFL= Y or N with IDB ADIS dataset submitted on 10.14.22, selected patients with 24 weeks of data.

8.5. Analysis of Submission-Specific Safety Issues

8.5.1. ARIA

Monoclonal antibodies directed against aggregated forms of beta amyloid, can cause ARIA, characterized as ARIA with edema (ARIA-E), observed on MRI as brain edema or sulcal effusions, and ARIA with hemosiderin deposition (ARIA-H), which includes microhemorrhage and superficial siderosis. ARIA-H can occur spontaneously in patients with Alzheimer's disease. ARIA-H of any cause and ARIA-E can occur together, and ARIA-H associated with monoclonal antibodies directed against aggregated forms of beta amyloid generally occurs in association with an occurrence of ARIA-E. ARIA is usually asymptomatic, although serious and life-threatening events, including seizure and status epilepticus, rarely can occur. Rarely, fatal outcomes have been observed in clinical trials of monoclonal antibodies directed against aggregated forms of beta amyloid. When present, reported symptoms associated with ARIA 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 following section focuses on findings of ARIA observed in donanemab clinical trials.

Summary

In blinded study AACI, three cases of ARIA had fatal outcome. No ARIA cases were reported to have fatal outcome in Study AACG or the all-donanemab pool. Serious ARIA-E cases were reported in 2% of donanemab-treated participants in Study AACG and 1% of participants in the all-donanemab-treated pool. ARIA occurred in 37% of donanemab-treated subjects compared to 8% of placebo in Study AACG. ARIA-E occurred in 27% in donanemab-treated participants compared to 1% of placebo in Study AACG. ARIA-H occurred in 30% in the donanemab arm compared to 7% on placebo in Study AACG. Symptomatic ARIA-E was reported in 3% of participants in the all-donanemab pool. No events of intracerebral hemorrhage > 1 cm were

reported in Study AACG. Three events of intracerebral hemorrhage > 1 cm were reported in the all-donanemab pool (0.2% [3/1304]).

Among donanemab-treated participants who experienced ARIA-E in Study AACG, 14% experienced symptoms. Symptoms reported in donanemab-treated participants with ARIA-E in Study AACG included headache and mental status changes. In the all-donanemab pool, 20% of donanemab-treated participants who experienced ARIA-E reported symptoms. The all-donanemab-treated pool showed similar findings compared to Study AACG of most frequent symptoms reported.

Among donanemab-treated participants in Study AACG, the maximum radiographic severity of ARIA-E was mild in 8%, moderate in 12%, and severe in 5% of participants. In the all-donanemab pool, 2% of participants had maximum radiographic severity of severe ARIA-E.

In participants who developed ARIA-E, approximately 95% experienced their first ARIA-E event by the 6th donanemab infusion in the all-donanemab pool. The first episode of ARIA-E had resolved by 20 weeks in 89% of donanemab-treated participants in Study AACG. Among donanemab-treated participants in Study AACG, 3% experienced more than one episode of ARIA-E.

In donanemab-treated participants in Study AACG, serious ARIA-E occurred at higher frequency in homozygous carriers for ApoE ϵ 4 compared to noncarriers (4% versus none, respectively). Donanemab-treated participants with concurrent antithrombotic use had similar frequencies of ARIA compared to participants without concurrent antithrombotic use in Study AACG. ARIA-E occurred with higher frequency in donanemab-treated participants < 75 years of age compared to $\geq$ 75 years of age in Study AACG and the all-donanemab treated pool. Higher frequencies of ARIA-E and ARIA-H was observed in donanemab-treated participants with microhemorrhage present at baseline compared to participants without microhemorrhage present at baseline in Study AACG and the all-donanemab pool.

Methods

In the key safety studies, ARIA events were recorded as adverse events and as MRI findings. ARIA-E findings were required to be reported as adverse events by investigators, but this was not specified for ARIA-H events. This reviewer considered the dataset containing MRI findings to be the more comprehensive dataset for ARIA findings and as a result, analyses in this section use the MRI dataset unless otherwise specified.

The reader is referred to the appendix for further details on the recording of ARIA events, reporting of ARIA in the adverse events dataset and MRI dataset, dose modification for ARIA, and indications related to ARIA leading to permanent treatment discontinuation.

Analyses Related to ARIA

In a response dated October 13, 2022, to an information request dated October 4, 2022, the sponsor presented analyses related to ARIA including the following:

- frequency of deaths, SAEs, discontinuations, and symptomatic events related to ARIA
- frequency of AEs by preferred terms reported as symptoms of ARIA
- frequency of ARIA by radiographic severity
- frequency of first ARIA-E event by infusion number
- time to resolution of ARIA-E
- frequency of subjects with resolution of symptoms of ARIA
- frequency of subjects with multiple episodes of ARIA-E
- frequency of concurrent and isolated events of ARIA
- frequency of ARIA by ApoE ϵ 4 carrier status, concomitant antithrombotic use, sex, age group, and presence of microhemorrhage on baseline MRI

Overall, this reviewer found the sponsor's analyses to be adequate.

ARIA-E occurred with frequency of 27% in the donanemab arm compared to 1% on placebo in Study AACG. ARIA-E was serious in 2% of donanemab-treated participants. The reader is referred to the [Narratives section](#) of the Serious Adverse Events section of this review for a review of narratives of serious ARIA. ARIA-E was symptomatic in 4% of donanemab-treated participants in Study AACG. ARIA-H occurred with frequency of 30% in the donanemab arm compared to 7% on placebo. ARIA-H microhemorrhage occurred with frequency of 20% in the donanemab arm compared to 5% on placebo, and ARIA-H superficial siderosis occurred with frequency of 17% in the donanemab arm compared to 2% on placebo.

Of note, the frequency of symptomatic ARIA noted in labeling is based on the frequency of symptomatic ARIA-E because symptoms of ARIA-H were not collected in Studies AACG, AACH, and AACI. One of the five donanemab-treated subjects with symptomatic ARIA-E was a homozygous carrier for ApoE ϵ 4, two were heterozygous for ApoE ϵ 4, and two were noncarriers. The reader is referred to the [Appendix](#) for a table that includes AE severity and radiographic severity in participants with symptomatic ARIA in Study AACG.

No ARIA events had fatal outcome in AACG. In the blinded main study of AACI, three cases of ARIA reported a fatal outcome ([15T-MC-AACI-\(b\) \(6\)](#) [15T-MC-AACI-\(b\) \(6\)](#) and Participant [\(b\) \(6\)](#) /Manufacturer Report # US202211015256. The reader is referred to the Deaths section of this review for further details of these cases. There were no events of intracerebral hemorrhage > 1 cm in Study AACG. The following table shows the frequency of ARIA events and intracerebral hemorrhage > 1 cm in Study AACG.

Table 38. Incidence of ARIA and Intracerebral Hemorrhage > 1 cm in Study AACG

ARIA Category	Donanemab N=131 n (%)	Placebo N=125 n (%)
ARIA	49 (37)	10 (8)
Deaths	0	0
SAEs	2 (2)	0
Study Withdrawal	6 (5)	1 (1)
Treatment Discontinuation	18 (14)	2 (2)
ARIA-E	35 (27)	1 (1)
Deaths	0	0
SAEs	2 (2)	0
Study Withdrawal	2 (2)	1 (1)
Treatment Discontinuation	7 (5)	1 (1)
Symptomatic ARIA-E ¹	5 (4)	1 (1)
ARIA-H	39 (30)	9 (7)
Deaths	0	0
SAEs	0	0
Study Withdrawal	5 (4)	0
Treatment Discontinuation	12 (9)	1 (1)
ARIA-H microhemorrhage	26 (20)	6 (5)
Deaths	0	0
SAEs	0	0
Study Withdrawal	3 (2)	0
Treatment Discontinuation	5 (4)	0
ARIA-H superficial siderosis	22 (17)	3 (2)
Deaths	0	0
SAEs	0	0
Study Withdrawal	1 (1)	0
Treatment Discontinuation	6 (5)	1 (1)
Intracerebral hemorrhage > 1 cm	0	0

¹The frequency of symptomatic ARIA is represented by symptomatic ARIA-E, because it includes participants who had ARIA-H. Symptoms of ARIA-H were not collected in Studies AACG, AACH, and AACI. The reviewer created this table using the IDB ADXP submitted on October 13, 2022, StudyID = AACG, PCSAFL from ADSL = Yes, TEPC57FL = yes, PARAM = severity of ARIA-E, ARIA-H MH, ARIA-H SS, or intracerebral hemorrhage.

In the all-donanemab pool at the time of the 90-Day Safety Update, no events of ARIA had fatal outcome. The frequency of serious ARIA-E cases was 1% and serious ARIA-H microhemorrhage and ARIA-H superficial siderosis cases was less than 1%. In the all-donanemab-treated pool, 3% of participants experienced symptomatic ARIA-E.

Three cases of intracerebral hemorrhage > 1 cm were reported in the all-donanemab pool at the time of the 90-Day Safety Update (0.2% [3/1304]: I5T-MC-AACI- (b) (6) I5T-MC-AACI- (b) (6) and I5T-MC-AACI- (b) (6)). In these cases, the participants did not receive additional doses of study drug after the events of intracerebral hemorrhage. One of the three cases was serious (I5T-MC-AACI- (b) (6)), and the reader is referred to the Narratives section of the Serious Adverse Events section of this review for a narrative for this case. The remaining two cases were non-serious and occurred in the setting of ongoing ARIA-E. The cases are summarized here.

Intracerebral Hemorrhage, I5T-MC-AACI- (b) (6) 58

An 81-year-old female, heterozygous for ApoE ε4, with hypertension, hyperlipidemia, and migraine who developed a 15 mm intracerebral hemorrhage in the left occipital region on Study Day 99 on a safety MRI. The patient was noted to have ARIA-E (right parietal and left occipital regions, severity of mild +), one new microhemorrhage, and one new superficial siderosis (20 mm) in the left occipital region on a safety MRI performed on Study Day 71. The screening MRI showed no evidence of ARIA-E or ARIA-H. The patient had received three doses of donanemab with the most recent dose 14 days prior to the MRI. The dose was interrupted because of the AEs of ARIA-H and asymptomatic ARIA-E. On Study Day 99, an unscheduled MRI showed persisting but decreased occurrence of ARIA-E (left occipital, mild severity), no new microhemorrhages or superficial siderosis, and the initial identification of the 15 mm intracerebral hemorrhage. On Study Day 127, an unscheduled MRI showed complete resolution of ARIA-E, no new microhemorrhages, and unchanged superficial siderosis, and a decrease in the size of the intracerebral hemorrhage to 11 mm. An MRI on Study Day 192 showed no change in findings compared to the previous MRI. The patient was discontinued from study treatment because dose stopping criteria were met and discontinued from the study due to physician decision on Study Day 197. The last dose of study drug was on Study Day 57. Concomitant medications included aspirin (81 mg daily), simvastatin, amlodipine, propranolol, hydrochlorothiazide, and lisinopril.

Reviewer comment: A role for donanemab in the event of intracerebral hemorrhage > 1 cm cannot be ruled out as the event occurred during an ongoing episode of ARIA-E. Additional risk factors for intracerebral hemorrhage >1 cm include hypertension, hyperlipidemia, and concomitant medication use with aspirin

Intracerebral hemorrhage, I5T-MC-AACI- (b) (6)

An 82-year-old female, heterozygous for ApoE ε4, with coronary artery disease, hypertension, hyperlipidemia, and chronic obstructive pulmonary disease was diagnosed with a non-serious AE of hemorrhagic stroke of moderate severity on Study Day 203 based on results of a safety

⁵⁸ The narrative for this participant is noted in a response dated July 1, 2022, to an information request dated June 29, 2022.

MRI performed the same day. The patient had received two doses of donanemab with the most recent dose occurring 174 days prior to the event (Study Day 29). The patient was diagnosed with the SAE of ARIA-E on Study Day 48. An unscheduled MRI on Study Day 49 showed severe ARIA-E and 7 new microhemorrhages (a screening MRI on Study Day -172 showed no findings of ARIA). The patient permanently discontinued from study treatment on Study Day 57. The final dose of donanemab was on Study Day 29. On Study Day 72, an unscheduled MRI showed moderate ARIA-E and 1 microhemorrhage. On Study Day 144, an MRI showed 4 new microhemorrhages, and three new areas of superficial siderosis. On Study Day 203, an MRI showed mild ARIA-E, 17 microhemorrhages, 2 new superficial siderosis, and one new frontal intracerebral hemorrhage measuring 35 mm in diameter. Concomitant medications included aspirin (81 mg daily), clonidine, diclofenac, hydrochlorothiazide, losartan, and nitroglycerin.

Reviewer comment: A role for donanemab in the event of intracerebral hemorrhage > 1 cm cannot be ruled out given the ongoing episode of ARIA-E. Additional risk factors for intracerebral hemorrhage >1 cm include hypertension, hyperlipidemia, coronary artery disease, and concomitant medication use with aspirin.

The sponsor noted one case that was initially classified as an intracerebral hemorrhage > 1 cm in the original submission and was reclassified as a subarachnoid hemorrhage at the time of the 90-Day Safety Update (15T-MC-AACI- (b) (6)), in a patient with likely contributory preceding events of fall.⁵⁹ This case is discussed further in the Serious Adverse Events section of this review.

The following table shows the frequency of ARIA events and intracerebral hemorrhage > 1 cm in the all-donanemab pool at the time of the 90-Day Safety Update. The decrease in incidence of ARIA compared to that observed in AACG may be in part because of a lower percentage of subjects in the all-donanemab pool with at least 6 months of exposure (81% [106/131] in Study AACG versus 63% [827/1304] in the all-donanemab pool).

Table 39. Frequency of ARIA and Intracerebral Hemorrhage > 1 cm in the All-Donanemab Pool at the 90-Day Safety Update

ARIA Category	Donanemab N=1304 n (%)
ARIA (-E and/or -H)	320 (25)
Deaths	0
SAEs	9 (1)

⁵⁹ Noted in the sponsor's response dated July 1, 2022, to an information request dated June 20, 2022.

ARIA Category	Donanemab N=1304 n (%)
Study Withdrawal	11 (1)
Treatment Discontinuation	31 (2)
ARIA-E	229 (18)
Deaths	0
SAEs	8 (1)
Study Withdrawal	7 (1)
Treatment Discontinuation	19 (1)
Symptomatic ARIA-E	45 (3)
ARIA-H	252 (19)
Deaths	0
SAEs	4 (<0.5)
Study Withdrawal	5 (<0.5)
Treatment Discontinuation	13 (1)
ARIA-H microhemorrhage	203 (16)
Deaths	0
SAEs	3 (<0.5)
Study Withdrawal	3 (<0.5)
Treatment Discontinuation	6 (<0.5)
ARIA-H superficial siderosis	105 (8)
Deaths	0
SAEs	0
Study Withdrawal	1 (<0.5)
Treatment Discontinuation	6 (<0.5)
Intracerebral hemorrhage > 1 cm	3 (<0.5)
Deaths	0
SAEs	1 (<0.5)
Study Withdrawal	0
Treatment Discontinuation	0

The reviewer created this table using the IDB ADXP submitted on October 13, 2022, LYMTRTL = Y, TELY57FL = yes, PARAM = severity of ARIA-E, ARIA-H MH, ARIA-H SS, or intracerebral hemorrhage.

In the sponsor's response dated November 1, 2022, to an information request dated October 31, 2022, the sponsor acknowledged that differences existed in the number of serious ARIA events reported in the MRI and AE datasets (8 events of serious ARIA-E versus 10 events of serious ARIA-E, respectively) in part because of differences in timing in when an MRI demonstrated an ARIA event and when an event was noted as serious by the investigator.

Of donanemab-treated participants who experienced ARIA-E in Study AACG, 14% experienced symptoms (5/35). Symptoms in donanemab-treated participants included headache, mental status changes, cognitive disorder, nausea/vomiting, fatigue, confusion, and expressive aphasia. Severity and seriousness of the symptoms of ARIA-E were not collected in Study AACG. No symptoms reported with ARIA-E belonged to the SMQ of convulsions. As noted previously, symptoms of ARIA-H were not collected in the studies; therefore, the frequency of symptomatic ARIA noted in labeling is based on the frequency of symptomatic ARIA-E.

Of participants who experienced ARIA-E in the all-donanemab pool, 20% experienced symptoms. The most frequent symptoms included headache and confusion/delirium/altered mental status/disorientation. Most of the symptoms were mild or moderate in severity.

No symptoms belonged to the SMQ of convulsions; however, the reviewer notes that two subjects who experienced ARIA events also experienced seizures. One of the two subjects experienced a concurrent event of ARIA-H (seizure, I5T-MC-AACI- (b) (6)). In this case, although a role for ARIA-H cannot be ruled out as the onset of the seizure was preceded by the development of ARIA-H, the event of subarachnoid hemorrhage was likely contributory to the SAE of seizure. This case is discussed further in the Narratives section of the Serious Adverse Events section of this review. In the second case, the non-serious seizure event had occurred 92 days after resolution of an ARIA-E event (partial seizures, I5T-MC-AACI- (b) (6)). A role for ARIA in the event of seizure was unlikely given lack of temporal association.

The following table shows symptoms with frequency of at least 1% in participants with ARIA-E in the all-donanemab pool at the time of the 90-Day Safety Update.

Table 40. Symptoms with Frequency of at Least 1% in Participants with ARIA-E in the All-Donanemab Pool at the 90-Day Safety Update

Category	DON-treated participants with ARIA-E N=229 n (%)
Subjects with symptomatic ARIA-E	45 (20)
Headache Fda B MQG	27 (12)
Headache	25 (11)
Tension Headache	2 (1)
Confusion, Delirium, Altered Mental Status, Disorientation, Coma MQG	10 (4)
Confusional State	7 (3)
Disorientation	1 (<0.5)

Category	DON-treated participants with ARIA-E N=229 n (%)
Disturbance In Attention	1 (<0.5)
Lethargy	1 (<0.5)
Mental Status Changes	3 (1)
Fall, Dizziness, Balance Disorder MQG	6 (3)
Balance disorder	1 (<0.5)
Dizziness	2 (1)
Gait disturbance	3 (1)
Aphasia	4 (2)
Asthenia, Fatigue, Malaise, Weakness, Narcolepsy MQG	3 (1)
Asthenia	1 (<0.5)
Fatigue	2 (1)
Amyloid related imaging abnormality-oedema/effusion	3 (1)
Cognitive disorder	3 (1)
Ataxia, Cerebellar Syndrome MQG	2 (1)
Ataxia	1 (<0.5)
Coordination abnormal	1 (<0.5)
Irritability Fda N MQG	2 (1)
Agitation	1 (<0.5)
Irritability	1 (<0.5)
Vision blurred	2 (1)
Symptomatic ARIA-E with mild symptoms	28 (12)
Symptomatic ARIA-E with moderate symptoms	11 (5)
Symptomatic ARIA-E with severe symptoms	1 (<0.5)

The reviewer created this table using the IDB ADAE_CE dataset submitted on 9.19.22, AEFORMNM=CE_AEA, TELY57FL=Y, grouped on USUBJID.

The following preferred terms of symptomatic ARIA-E were reported in less than 1% of subjects with ARIA-E in the all-donanemab pool at the time of the 90-Day Safety Update (one participant each): Agitation, Asthenia, Ataxia, Balance disorder, Bradyphrenia, Communication disorder, Coordination abnormal, Decreased appetite, Disorientation, Disturbance in attention, Dyslexia, Dysphagia, Dyspnea, Eye movement disorder, Hyperhidrosis, Hyporesponsive to stimuli, Intellectual disability, Irritability, Lethargy, Nausea, Psychomotor retardation, Tremor, Visual agnosia, and Vomiting.

Among donanemab-treated participants who experienced ARIA-E, 11% experienced symptoms with the first event (4/35). Four subjects experienced a second event of ARIA-E, of which none were symptomatic. The lower likelihood of experiencing symptoms with the second event of ARIA-E is likely in part driven by protocol as patients with SAEs of ARIA-E were required to permanently discontinue treatment.

Similar findings were observed in the all-donanemab pool. Among participants in the all-donanemab pool who experienced ARIA-E, 10% (22/229) experienced symptoms with the first event (22/229) compared to no subjects with the second event.⁶⁰

The following table shows the frequency of symptomatic ARIA-E in subjects by ARIA-E event numbers in Study AACG.

Table 41. Frequency of Symptomatic ARIA-E in Subjects Who Experienced ARIA-E in Study AACG.

ARIA-E Event Number Symptomatic Status	Subjects on Donanemab Who Experienced ARIA-E N=35 n (%)
First Event of ARIA-E Symptomatic	4/35 (11)
Second Event of ARIA-E Symptomatic	0/4 (0)

Symptomatic status for the first event of ARIA-E was obtained by joining IDB ADXP submitted on October 13, 2022, StudyID = AACG, LYMTRTL=Y, PARAM = Presence of ARIA-E, TEPC57FL = yes, grouped on USUBJID, TRTA, and minimum of ADY and joined with the CE dataset submitted on 8.17.22, CECAT = ARIAE, STUDYID = AACG by USUBJID. ARIA-E was defined as symptomatic if symptoms occurred 7 days before or after the start of ARIA-E. Symptomatic status for the second event of ARIA-E was obtained by joining IDB ADTTE submitted on September 19, 2022, PCSAFL=Y, PARAM=Time of ARIA-E resolution in days, CNSR=0, with the CE dataset submitted on 8.17.22, CECAT = ARIAE, STUDYID = AACG by USUBJID (do not include matches).

Among participants treated with donanemab, the maximum radiographic severity of ARIA-E was mild in 8%, moderate in 12%, and severe in 5% of participants. The following table shows the maximum radiographic severity of ARIA in Study AACG.

Table 42. Maximum Radiographic Severity of ARIA Events in Subjects with Mild, Moderate, or Severe Radiographic Categories of ARIA in Study AACG

ARIA Severity	Donanemab N=131	Placebo N=125

⁶⁰ Information noted on pages 102 and 104 of the sponsor's response dated October 13, 2022 to an information request dated October 4, 2022

ARIA-E ¹	35 (27)	1 (1)
Mild	11 (8)	0
Moderate	16 (12)	1 (1)
Severe	7 (5)	0
ARIA-H Microhemorrhage	26 (20)	6 (5)
Mild	19 (15)	6 (5)
Moderate	2 (2)	0
Severe	5 (4)	0
ARIA-H Superficial siderosis	22 (17)	3 (2)
Mild	12 (9)	2 (2)
Moderate	3 (2)	1 (1)
Severe	7 (5)	0

¹Cases of ARIA-E could be adjudicated as mild, moderate, severe, or questionable. The reviewer created this table using the IDB ADXP submitted on October 13, 2022, StudyID = AACG, PCSAFL from ADSL = Yes, TEPC57FL = yes, PARAM = Severity of ARIA-E or ARIA-H Microhemorrhage or ARIA-H Superficial siderosis, AVISIT = Postbaseline MAX PC57, grouped on USUBJID and TRTA.

In the all-donanemab pool, the maximum radiographic severity was severe in 2% of ARIA-E events and 4% of ARIA-H events. The following table shows the maximum radiographic severity of ARIA in the all-donanemab pool at the time of the 90-Day Safety Update.

Table 43. Maximum Radiographic Severity of ARIA Events in Subjects with Mild, Moderate, or Severe Radiographic Categories of ARIA in the All-Donanemab Pool at the 90-Day Safety Update

ARIA Severity	Donanemab N=1304
ARIA-E	229 (18)
Mild	89 (7)
Moderate	118 (9)
Severe	21 (2)
ARIA-H Microhemorrhage	203 (16)
Mild	148 (11)
Moderate	24 (2)
Severe	31 (2)
ARIA-H Superficial siderosis	105 (8)
Mild	60 (5)
Moderate	22 (2)
Severe	23 (2)

The reviewer created this table using the IDB ADXP submitted on October 13, 2022, LYMTRTL = Y, TELY57FL = Y, PARAM = Severity of ARIA-E or ARIA-H Microhemorrhage or ARIA-H Superficial siderosis, AVISIT = Postbaseline MAX LY57, grouped on USUBJID.

Approximately 80% of ARIA-E events occurred by the sixth donanemab infusion. The following table shows the percentage of donanemab-treated participants with first ARIA-E event by infusion number in Study AACG. Based on these observations, it is reasonable to recommend MRIs to evaluate for ARIA prior to the 2nd, 3rd, 4th, and 7th infusions.

Table 44. Percentage of Donanemab-treated Participants with First ARIA-E event by Donanemab Infusion Number in Study AACG.

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

The reviewer created this table using the IDB ADXP submitted on October 13, 2022, PCSAFL from ADSL = Yes, TEPC57FL = yes, PARAM = severity of ARIA-E, DTYPE = null, TRTA = Donanemab, grouped on USUBJID and minimum of ADY, joined with the IDB ADEX submitted on 8.25.22, PARAM = Exposure infusion (ml), EXTRT = DON, and EXDOSE= inverse of 0.

Approximately 95% of ARIA-E events occurred by the sixth donanemab infusion in the all-donanemab pool. The following table shows the percentage of participants with first ARIA-E event by infusion number in the all-donanemab pool at the time of the 90-Day Safety Update.

Table 45. Percentage of Participants with First ARIA-E event by Donanemab Infusion Number in All-Donanemab Pool at the 90-Day Safety Update.

Number of Donanemab Infusions	# of Participants with First ARIA-E Event	Cumulative # Participants with 1st ARIA-E Event	Cumulative % of Participants with 1st ARIA-E Event	# of Participants with First Serious ARIA-E Event
1	31	31	14	0

Number of Donanemab Infusions	# of Participants with First ARIA-E Event	Cumulative # Participants with 1st ARIA-E Event	Cumulative % of Participants with 1st ARIA-E Event	# of Participants with First Serious ARIA-E Event
2	25	56	24	4
3	108	164	72	4
4	7	171	75	0
5	9	180	79	0
6	38	218	95	0
7	6	224	98	0
8	0	224	98	0
9	3	227	99	0
10	0	227	99	0
11	0	227	99	0
12	0	227	99	0
13	2	229	100	0

The reviewer created this table using the IDB ADXP submitted on October 13, 2022, LYMTRTFL = Y, TELY57FL = Y, PARAM = severity of ARIA-E, DTYPE = null, grouped on USUBJID and minimum of ADY, joined with the IDB ADEX submitted on 8.25.22, PARAM = Exposure infusion (ml), EXTRT = DON, and EXDOSE= inverse of 0.

The median duration of the first episode of ARIA-E in donanemab-treated participants in Study AACG was 70 days. The following table shows the duration (days) of the first episode of ARIA-E in Study AACG.

Table 46. Duration of First Episode of ARIA-E in Study AACG

Duration (days)	DON N=131	Placebo N=125
n (%)	35 (27)	1 (1)
Mean (SD)	80 (44)	165 (n/a)
Median (Min, Max)	70 (29, 212)	165 (165, 165)

The reviewer created this table using the IDB ADTTE submitted on September 19, 2022, PCSAFL=Y, PARAM=Time of ARIA-E resolution in days.

The median duration of the first episode of ARIA-E in participants in the all-donanemab pool was 57 days. The following table shows the duration (days) of the first episode of ARIA-E in the all-donanemab pool at the time of the 90-Day Safety Update.

Table 47. Duration of First Episode of ARIA-E in All-Donanemab Pool at the 90-Day Safety Update

Duration (days)	DON N=1304
n (%)	229 (18)
Mean (SD)	60 (35)
Median (Min, Max)	57 (2, 212)

The reviewer created this table using the IDB ADTTE submitted on September 19, 2022, LYMTFTL=Y, PARAM=Time of ARIA-E resolution in days.

The first episode of ARIA-E had resolved by 12 weeks in 66% of donanemab-treated participants and by 20 weeks in 89% of donanemab-treated participants in Study AACG. The following table shows time to resolution of first event of ARIA-E by Weeks 12, 20, and the end of the study in Study AACG.

Table 48. Time to Resolution of First Event of ARIA-E in Study AACG

Time to Resolution	Donanemab		Placebo	
	# First ARIA-E events resolved n	% (# First ARIA-E events resolved/# of Persons with ARIA-E) N=35	# First ARIA-E events resolved n	% (# First ARIA-E events resolved/# of Persons with ARIA-E) N=1
12 weeks	23	66	0	0
20 weeks	31	89	0	0
End of Study	35	100	1	100

The reviewer created this table using ADTTE submitted on September 19, 2022, PCSAFL = Y, PARAM = Time of ARIAE Resolution (Days) PC in TRT + 57 days, CNSR = 0, grouped on USUBJID and MIN of ADT, then joined to previous table, with AVAL/7 = < 12 for 12 weeks, < 20 for 20 weeks.

The first episode of ARIA-E had resolved by 12 weeks in 54% of donanemab-treated participants and by 20 weeks in 69% of donanemab-treated participants in the all-donanemab pool. The following table shows time to resolution of first event of ARIA-E by Weeks 12, 20, and the end of the study in the all-donanemab pool at the time of the 90-Day Safety Update.

Table 49. Time to Resolution of First Event of ARIA-E in All-Donanemab Pool at the 90-Day Safety Update

Time to Resolution	Donanemab	
	# First ARIA-E events resolved n	% (# First ARIA-E events resolved/# of Persons with ARIA-E) N=229
12 weeks	123	54
20 weeks	157	69
End of Study	162	71

The reviewer created this table using ADTTE submitted on September 19, 2022, LYMTRTFL = Y, PARAM = Time of ARIAE Resolution (Days) LY in TRT + 57 days, CNSR = 0, grouped on USUBJID and MIN of ADT, then joined to previous table, with AVAL/7 = < 12 for 12 weeks, < 20 for 20 weeks.

Of the five donanemab-treated participants who experienced symptomatic ARIA-E in Study AACG, two experienced complete resolutions of their symptoms of ARIA-E (40%).⁶¹

Of the participants who experienced symptomatic ARIA-E in the all-donanemab pool at the time of the 90-Day Safety Update, 56% experienced complete resolutions of their symptoms of ARIA-E (25/45).⁶²

Among donanemab-treated participants in Study AACG, 3% experienced more than one episode of ARIA-E. The following table shows the frequency of subjects with multiple episodes of ARIA-E in Study AACG.

Table 50. Frequency of Subjects with Multiple Episodes of ARIA-E in Study AACG.

Number of ARIA-E episodes	Donanemab N=131 n (%)	Placebo N=125 n (%)
1	31 (24)	1 (1)
2	4 (3)	0
3	0	0

The reviewer created the table using ADTTE submitted on September 19, 2022, PCSAFL = Y, PARAM = Time of ARIAE Resolution (Days) PC in TRT + 57 days, CNSR = 0, grouped on USUBJID and TRTA, the distribution of "N rows." Selected 1 for 1 episode of ARIA-E, 2 for two episodes of ARIA-E, and 3 or more for three or more episodes of ARIA-E.

⁶¹ ADAE_CE dataset submitted on 9.19.22, AEFORMMN = CE_ARIAE, TEPC57FL=Y, AEENDTC = all.

⁶² ADAE_CE dataset submitted on 9.19.22, AEFORMMN = CE_ARIAE, TELY57FL=Y, AEENDTC = all.

Among participants in the all-donanemab pool, 1% experienced more than one episode of ARIA-E. The following table shows the frequency of subjects with multiple episodes of ARIA-E in the all-donanemab pool at the time of the 90-Day Safety Update.

Table 51. Frequency of Subjects with Multiple Episodes of ARIA-E in All-Donanemab Pool at the 90-Day Safety Update.

Number of ARIA-E episodes	Donanemab N=1304 n (%)
1	210 (16)
2	18 (1)
3	1 (<0.5)

The reviewer created the table using ADTTE submitted on September 19, 2022, LYMTTRFL = Y, PARAM = Time of ARIAE Resolution (Days) LY in TRT + 57 days, CNSR = 0 concatenated with ADTTE submitted on September 19, 2022, LYMTTRFL = Y, PARAMCD = OARRLi57, grouped on USUBJID, distribution of "N rows." Selected 1 for 1 episode of ARIA-E, 2 for two episodes of ARIA-E, and 3 or more for three or more episodes of ARIA-E.

In a January 13, 2023, response to an information request, the sponsor submitted data showing limited experience in continuing to administer donanemab in a patient with an ongoing episode of ARIA, and no experience in patients with ongoing severe ARIA.

ARIA-E or ARIA-H may occur in isolation or concurrently. ARIA-H occurring with ARIA-E has been noted in studies of other monoclonal antibodies. For example, in participants receiving bapineuzumab in two Phase 2 studies and one open-label extension study, incident ARIA-H occurred in 47% (17/36) of ARIA-E cases compared to 4% (7/177) of cases without ARIA-E. In the majority of cases, ARIA-H occurred on the same MRI or on an MRI scan immediately before or after the MRI with ARIA-E (14/17) and occurred in the same region as ARIA-E (8/14).⁶³ In two Phase 3 studies of aducanumab, the incidence of brain microhemorrhages and localized superficial siderosis was increased in participants with ARIA-E compared with participants without ARIA-E. In participants without ARIA-E, the incidence of brain microhemorrhage and localized superficial siderosis was similar between the aducanumab and placebo groups.⁶⁴

As noted by Sperling et al., ARIA-H occurring with ARIA-E suggests a shared pathophysiological mechanism and may be related to transient increases in vascular permeability. As postulated by Sperling et al, it is possible that depending on the location of the vessel, in the parenchyma

⁶³ Sperling et al. Amyloid-related imaging abnormalities in patients with Alzheimer's disease treated with bapineuzumab: a retrospective analysis. *Lancet Neurol.* 2012 March; 11(3): 241–249.

⁶⁴ Salloway et al. Amyloid-Related Imaging Abnormalities in 2 Phase 3 Studies Evaluating Aducanumab in Patients with Early Alzheimer's Disease. *Jama Neurology.* JAMA Neurol. 2022;79(1):13-21.
doi:10.1001/jamaneurol.2021.416

versus meninges, leakage of proteinaceous fluid could give lead to an increased signal on FLAIR images (ARIA-E) in the brain parenchyma (vasogenic edema) and leptomeningeal spaces (sulcal effusions), while leakage of red cells would result in ARIA-H, seen on T2*-weighted gradient echo MRI as cerebral microhemorrhages and hemosiderosis.⁶³

In the donanemab arm of Study AACG, 18% of participants experienced concurrent ARIA-E and ARIA-H, defined as ARIA-E occurring on the same MRI as ARIA-H.

In donanemab-treated participants in Study AACG, ARIA-H was more likely to occur as an isolated event, defined as ARIA-H occurring during the study and not ARIA-E, among participants with ARIA-H compared to isolated ARIA-E among participants with ARIA-E. In donanemab-treated participants who experienced ARIA-H in Study AACG, 36% experienced isolated ARIA-H (14/39). In donanemab-treated participants who experienced ARIA-E in Study AACG, 29% experienced isolated ARIA-E (10/35).

The following table shows the frequency of participants experiencing concurrent and isolated ARIA in Study AACG.

Table 52. Frequency of Concurrent and Isolated ARIA in Study AACG¹

ARIA Category	Donanemab N=131 n (%)	Placebo N=125 n (%)
ARIA-E or ARIA-H	49 (37)	10 (8)
Concurrent ARIA-E and ARIA-H ²	23 (18)	0
ARIA-E	35 (27)	1 (1)
Isolated ARIA-E ³	10 (8)	1 (1)
ARIA-H	39 (30)	9 (7)
Isolated ARIA-H ⁴	14 (11)	9 (7)

¹One event of ARIA-E of questionable severity occurring in a donanemab-treated participant was included in this table.

²Concurrent ARIA-E and ARIA-H is defined as a subject having ARIA-E and ARIA-H on the same MRI.

³Isolated ARIA-E is defined as participants who had only ARIA-E and not ARIA-H during the study.

⁴Isolated ARIA-H is defined as participants who had only ARIA-H and not ARIA-E during the study.

The reviewer created this table using the IDB ADXP submitted on October 13, 2022, StudyID = AACG, PCSAFL from ADSL = Yes, TEPC57FL = yes, PARAM = set to ARIA categories.

In the all-donanemab pool, ARIA-E was more likely to occur as an isolated event among participants with ARIA-E compared to isolated ARIA-H among participants with ARIA-H. In participants who experienced ARIA-H in the all-donanemab pool, 29% experienced isolated ARIA-H (67/229). In participants who experienced ARIA-E in the all-donanemab pool, 36% experienced isolated ARIA-E (91/252). The following table shows the frequency of participants

experiencing concurrent and isolated ARIA in the all-donanemab pool at the time of the 90-Day Safety Update.

Table 53. Frequency of Concurrent and Isolated ARIA in All-Donanemab Pool at the 90-Day Safety Update¹

ARIA Category	Donanemab N=1304 n (%)
ARIA-E or ARIA-H	320 (25)
Concurrent ARIA-E and ARIA-H ²	122 (9)
ARIA-E	229 (18)
Isolated ARIA-E ³	67 (5)
ARIA-H	252 (19)
Isolated ARIA-H ⁴	91 (7)

¹One event of ARIA-E of questionable severity was included in this table.

²Concurrent ARIA-E and ARIA-H defined as a subject having ARIA-E and ARIA-H on the same MRI.

³Isolated ARIA-E is defined as participants who had only ARIA-E and not ARIA-H during the study.

⁴Isolated ARIA-H is defined as participants who had only ARIA-H and not ARIA-E during the study.

The reviewer created this table using the IDB ADXP submitted on October 13, 2022, LYMTRTL = Y, TELY57FL = yes, PARAM = set to ARIA categories.

ARIA by Subgroups

In donanemab-treated participants in Study AACG, ARIA-E and ARIA-H occurred with higher frequency in homozygous carriers compared to heterozygous carriers and noncarriers. Serious ARIA-E occurred at higher frequency in homozygous and heterozygous carriers for ApoE ε4 compared to noncarriers (4% and 1% versus none, respectively). Radiographically severe ARIA was observed at higher frequencies in homozygote carriers compared to noncarriers in the donanemab-treated arm of Study AACG (ARIA-E: 12% versus 6%, ARIA-H: 20% versus 6%, respectively). Similar findings were observed for the all-donanemab pool (the reader is referred to the [Appendix](#) for findings in the all-donanemab pool). The following table shows serious ARIA events and ARIA events by radiographic severity and ApoE ε4 carrier status in Study AACG.

Table 54. Serious ARIA and Radiographic Severity of ARIA by ApoE ε4 Carrier Status in Study AACG.

Category	Donanemab N=131			Placebo N=125		
	NC N=36 n (%)	HET N=70 n (%)	HOM N=25 n (%)	NC N=32 n (%)	HET N=64 n (%)	HOM N=28 n (%)
ARIA	7 (19)	25 (36)	17 (68)	2 (6)	4 (6)	4 (14)
ARIA-E	3 (8)	21 (30)	11 (44)	0	0	1 (4)

Category	Donanemab N=131			Placebo N=125		
	NC N=36 n (%)	HET N=70 n (%)	HOM N=25 n (%)	NC N=32 n (%)	HET N=64 n (%)	HOM N=28 n (%)
Serious ARIA-E	0	1 (1)	1 (4)	0	0	0
Mild	0	9 (13)	2 (8)	0	0	0
Moderate	0	10 (14)	6 (24)	0	0	1 (4)
Severe	2 (6)	2 (3)	3 (12)	0	0	0
ARIA-H	7 (19)	15 (21)	17 (68)	2 (6)	4 (6)	3 (11)
Serious ARIA-H	0	0	0	0	0	0
Mild	4 (11)	10 (14)	9 (36)	2 (6)	4 (6)	2 (7)
Moderate	1 (3)	1 (1)	3 (12)	0	0	1 (4)
Severe	2 (6)	4 (6)	5 (20)	0	0	0

HET: heterozygous status, HOM: homozygous status, NC: noncarrier status. Mild, moderate, and severe categories are based on maximum radiographic severity.

There were no exclusion criteria related to antithrombotics use in Study AACG. Taking into consideration differences observed with placebo, a similar frequency of ARIA-H microhemorrhage and ARIA-H superficial siderosis was observed in the donanemab-treated arm in participants with concomitant antithrombotic use compared to participants without concomitant anti-thrombotic use in Study AACG. In the all-donanemab pool, a higher frequency of ARIA events was not reported in participants with concurrent antithrombotic use compared to participants without concurrent use. The following table shows the frequency of ARIA events based on concomitant antithrombotic use within 30 days prior to onset of the event. The reader is referred to the [Appendix](#) for findings in the all-donanemab pool.

Table 55. Frequency of ARIA and Intracerebral hemorrhage > 1 cm based on Concomitant Antithrombotic Medication Use in Study AACG¹.

Event	Antithrombotic Use	Donanemab N=131	Placebo N=125
ARIA	Yes	22 (17)	7 (6)
	No	27 (21)	3 (2)
ARIA-E	Yes	17 (13)	0
	No	18 (14)	1 (1)
ARIA-H	Yes	20 (15)	7 (6)
	No	19 (15)	2 (2)
ARIA-H Microhemorrhage	Yes	12 (9)	4 (3)
	No	14 (11)	2 (2)

Event	Antithrombotic Use	Donanemab N=131	Placebo N=125
ARIA-H Superficial siderosis	Yes	13 (10)	3 (2)
	No	9 (7)	0
Intracerebral hemorrhage > 1 cm	Yes	0	0
	No	0	0

¹Antithrombotic use considered concomitant when occurring within 30 days prior to onset of event. The reviewer created this table using the IDBDXP submitted on October 13, 2022, StudyID = ACG, PCSAFL from ADSL = Yes, TEPC57FL = yes, PARAM = Severity of ARIA event joined with IDB ADCM submitted on August 25, 2022, ANTITHFL=Y, PCIN57FL=Y.

Acetylsalicylic acid was the most frequently occurring antithrombotic used in Study AACG and the all-donanemab pool (82% [54/66]). The following table shows the frequency of subjects with use of antithrombotic medications at any point during Study AACG or within 57 days of the end of the study. The reader is referred to the [Appendix](#) for findings in the all-donanemab pool.

Table 56. Frequency of Subjects with Antithrombotic Medication Use in Study AACG

Category	DON N=131 n (%)	Placebo N=125 n (%)
Antithrombotic	66 (50)	70 (56)
Acetylsalicylic acid-containing products	54 (41)	56 (45)
Non-acetylsalicylic acid antiplatelets	6 (5)	7 (6)
Anticoagulants	19 (15)	22 (18)

Medications were used at any time during Study AACG or within 57 days of the end of the study. The reviewer created this table using the ADCM submitted on August 25, 2022, ADSL.PCSAFL=Y, PCIN57FL=Y, ANTITHFL=Y, grouped on USUBJID and TRTA.

In donanemab-treated participants in Study AACG, ARIA-H microhemorrhage occurred at higher frequency in males compared to females (27% versus 13%, respectively). In the all-donanemab pool, ARIA-E, ARIA-H and intracerebral hemorrhage > 1 cm occurred with similar frequency between females and males (difference ≤ 3%). The following table shows frequency of ARIA and intracerebral hemorrhage > 1 cm based on sex in Study AACG. The reader is referred to the [Appendix](#) for findings with the all-donanemab pool.

Table 57. Frequency of ARIA and Intracerebral hemorrhage > 1 cm Based on Sex in Study AACG

Event	DON N=131		Placebo N=125	
	Female N=68 n (%)	Male N=63 n (%)	Female N=64 n (%)	Male N=61 n (%)
ARIA	26 (38)	23 (37)	4 (6)	6 (10)
ARIA-E	20 (29)	15 (24)	0	1 (2)
ARIA-H	16 (24)	23 (37)	4 (6)	5 (8)
ARIA-H Microhemorrhage	9 (13)	17 (27)	3 (5)	3 (5)
ARIA-H Superficial siderosis	11 (16)	11 (17)	1 (2)	2 (3)
Intracerebral hemorrhage > 1 cm	0	0	0	0

The reviewer created this table using the IDB ADXP submitted on October 13, 2022, StudyID = AACG, PCSAFL from ADSL = Yes, TEPC57FL = yes, PARAM = Severity of ARIA-E, ARIA-H, ARIA-H MH, and ARIA-H SS, then grouped on USUBJID, PARAM, SEX, and TRTA.

ARIA-E occurred with higher frequency in donanemab-treated participants < 75 years of age compared to ≥75 years of age in Study AACG (32% versus 23%, respectively). Similar findings of a higher frequency of ARIA-E in the younger age group were observed in the all-donanemab pool. The following table shows the frequency of ARIA and intracerebral hemorrhage > 1 cm based on age group < 75 and ≥75 years of age in Study AACG. The reader is referred to the [Appendix](#) for findings with the all-donanemab pool.

Table 58. Frequency of ARIA and Intracerebral hemorrhage > 1 cm Based on Age Group in Study AACG

Event	DON N=131		Placebo N=125	
	< 75 years N=60 n (%)	≥75 years N=71 n (%)	< 75 years N=51 n (%)	≥75 years N=74 n (%)
ARIA	22 (37)	27 (38)	3 (6)	7 (9)
ARIA-E	19 (32)	16 (23)	1 (2)	0
ARIA-H	17 (28)	22 (31)	2 (4)	7 (9)
ARIA-H Microhemorrhage	11 (18)	15 (21)	1 (2)	5 (7)
ARIA-H Superficial siderosis	11 (18)	11 (15)	1 (2)	2 (3)
Intracerebral hemorrhage > 1 cm	0	0	0	0

The reviewer created this table using the IDB ADXP submitted on October 13, 2022, StudyID = AACG, PCSAFL from ADSL = Yes, TEPC57FL = yes, PARAM = Severity of ARIA-E , ARIA-H, ARIA-H MH, and ARIA-H SS, then grouped on USUBJID, PARAM, AGEGR2, and TRTA.

Higher frequencies of ARIA-E and ARIA-H was observed in donanemab-treated participants with microhemorrhage present at baseline compared to participants without microhemorrhage present at baseline in Study AACG and the all-donanemab pool. The following table shows the frequency of ARIA based on presence of microhemorrhage on baseline MRI in Study AACG. The reader is referred to the [Appendix](#) for findings with the all-donanemab pool.

Table 59. Frequency of ARIA and Intracerebral Hemorrhage > 1 cm Based on Presence of Microhemorrhage at Baseline in Study AACG

Event	DON N=131		Placebo N=125	
	BMH Not Present N=113 n (%)	BMH Present N=18 n (%)	BMH Not Present N=101 n (%)	BMH Present N=24 n (%)
ARIA	34 (30)	15 (83)	8 (8)	2 (8)
ARIA-E	27 (24)	8 (44)	1 (1)	0
ARIA-H	24 (21)	15 (83)	7 (7)	2 (8)
ARIA-H Microhemorrhage	15 (13)	11 (61)	5 (5)	1 (4)
ARIA-H Superficial siderosis	13 (12)	9 (50)	2 (2)	1 (4)
Intracerebral hemorrhage > 1 cm	0	0	0	0

BMH: baseline microhemorrhage. The reviewer created this table using the IDB ADXP submitted on October 13, 2022, StudyID = AACG, PCSAFL = Y, PARAM = number of microhemorrhages present, ABLFL=Y, where Yes = AVAL = 1 through 4 and No = AVAL = 0, joined with IDB ADXP submitted on October 13, 2022, StudyID = AACG, PCSAFL = Y, TEPC57FL=Y, PARAM = severity of ARIA-E and ARIA-H, grouped on USUBJID, AVAL, and TRTA.

The impact of brain volume changes with donanemab treatment in relation to clinical outcomes is addressed in the efficacy review by Dr Kevin Krudys.

In summary, ARIA-E and ARIA-H were reported with higher frequency in donanemab-treated participants compared to placebo in Study AACG. In blinded study AACI, three cases of ARIA had fatal outcome. Serious ARIA-E cases were reported with low frequency in donanemab-treated participants (1% in the all-donanemab pool). The frequency of intracerebral hemorrhage > 1 cm in donanemab-treated participants was low (0% [3/1304] in the all-donanemab pool). Symptomatic ARIA-E was reported in 3% of participants in the all-donanemab pool, 20% reported symptoms. The most frequent symptoms reported with ARIA-E were headache and mental status changes. In participants who developed ARIA-E, approximately 95% experienced their first ARIA-E event by the 6th donanemab infusion in the all-donanemab pool. Donanemab-

treated participants with concurrent antithrombotic use had similar frequencies of ARIA and intracerebral hemorrhage > 1 cm compared to participants without concurrent antithrombotic use in Study AACG. Higher frequencies of ARIA-E were observed in donanemab-treated participants < 75 years of age compared to ≥75 years of age. Higher frequencies of ARIA-E and ARIA-H was observed in donanemab-treated participants with microhemorrhage present at baseline compared to participants without microhemorrhage present at baseline.

8.5.2. Hypersensitivity and Infusion Related Reactions

Serious cases of infusion related reaction were reported with 2% frequency in the donanemab arm compared to none on placebo in Study AACG. Serious cases of anaphylaxis were also reported in Phase 2 and 3 studies. A review of narratives of participants with infusion related reactions identified cases with increases and decreases in blood pressure and increases in heart rate at the time of infusion or within minutes following the end of the infusion. Infusion related reaction was among the most frequently reported TEAE in Study AACG, occurring in 8% of donanemab-treated subjects compared to none on placebo. Most TEAEs related to hypersensitivity and infusion-related reactions were mild or moderate in severity in Study AACG and the all-donanemab pool. Infusion related reaction was the most frequently reported TEAE leading to study withdrawal and treatment discontinuation, which was in part driven by protocol.

The sponsor evaluated the frequency of TEAEs belonging to the SMQs of Anaphylactic Reaction, Hypersensitivity, and Angioedema and occurrence of AEs within 24 hours of an infusion or > 24 hours from an infusion.

Overall, the reviewer found the sponsor’s approach to be acceptable.

Participants in donanemab and placebo arms of Study AACG reported SAEs belonging to the SMQs of Anaphylactic Reaction, Hypersensitivity, and Angioedema (Narrow) with the same frequency (2%). Infusion related reaction was the most frequently reported SAE in the donanemab arm, occurring in two participants (2%) compared to none on placebo. The following table shows the frequency of SAEs by preferred term belonging to the SMQ of Anaphylactic Reaction, Hypersensitivity, and Angioedema (Narrow) in Study AACG.

Table 60. SAEs Belonging to the SMQs of Anaphylactic Reaction, Hypersensitivity, and Angioedema (Narrow) in Study AACG

Preferred Term	DON N=131 n (%)	Placebo N=125 n (%)
Subject Reporting at least one SAE	3 (2)	3 (2)
Infusion related reaction	2 (2)	0

Preferred Term	DON N=131 n (%)	Placebo N=125 n (%)
Drug eruption	1 (1)	0
Cardiac arrest	0	1 (1)
Hypotension	0	1 (1)
Mouth swelling	0	1 (1)
Pharyngeal swelling	0	1 (1)

The reviewer created this using the IDB ADAE dataset submitted 8.25.22, SAFFL = Yes, StudyID=AACG, PCIN57FL = Yes, TRTEMFL = yes, AESER=Y, new column with below formula, SMQ12SC through 14SC not equal to broad, grouped on USUBJID, AEDECOD, TRT01A

In the all-donanemab pool at the 90-Day Safety Update, 1% (9/1304) of participants reported an SAE belonging to the SMQ of Anaphylactic Reaction, Hypersensitivity, and Angioedema (Narrow). The most frequent SAE reported was infusion related reaction (5/1304; less than 0.5%) followed by anaphylactic reaction (3/1304; less than 0.5%) and drug eruption (1/1304; less than 0.5%).

In Study AACG, infusion related reaction was among the most frequent TEAEs reported to lead to study withdrawal (4% [5/131] versus none [0/125], respectively) and treatment discontinuation (5% [7/131] versus none [0/125], respectively) in the donanemab arm compared to placebo. The higher frequency was likely, in part, driven by study protocol, which noted that donanemab was to be permanently discontinued in patients with prolonged acute infusion reaction. In the all-donanemab pool, infusion related reaction was reported to lead to study withdrawal in 2% of participants (20/1304) and treatment discontinuation in 3% of participants (35/1304).

Infusion related reaction was among the most frequently reported TEAEs in Study AACG, occurring in 8% (10/131) of donanemab-treated participants compared to none (0/125) on placebo. In the all-donanemab pool, infusion related reaction was reported in 9% (115/1304) of participants at the time of the 90-Day Safety Update. For symptoms associated with infusion related reactions, the reader is referred to narratives of SAEs of infusion related reactions, the narrative for [I5T-MC-AACG-](#) (b) (6) Table 66. Cases Related to the Topic of Anaphylactic Reaction in Phase 2 and 3 Studies, and Table 67. Infusion Related Reactions and Associated Blood Pressure Changes After Infusion Initiation in Three Participants in Phase 2 and 3 Studies.

A higher frequency of TEAEs belonging to the SMQ Hypersensitivity (narrow) with onset within 24 hours after an infusion was reported in the donanemab arm compared to placebo (8% versus 2%, respectively). The following table shows the frequency of TEAEs Belonging to the SMQs of Anaphylactic Reaction, Hypersensitivity, and Angioedema (Narrow) in Study AACG.

Table 61. Frequency of TEAEs Belonging to the SMQs of Anaphylactic Reaction, Hypersensitivity, and Angioedema (Narrow) in Study AACG

SMQ, Onset ¹	DON N=131 n (%)	Placebo N=125 n (%)
Anaphylactic reaction, ≤ 24 hours	0	0
Anaphylactic reaction, > 24 hours	0	0
Hypersensitivity, ≤ 24 hours	10 (8)	2 (2)
Hypersensitivity, > 24 hours	6 (5)	13 (10)
Angioedema, ≤ 24 hours	0	1 (1)
Angioedema, > 24 hours	1 (1)	2 (2)

¹TEAE onset from the time of the donanemab infusion. The reviewer created this table using the IDB ADAE dataset submitted 8.25.22, SAFFL = Yes, StudyID=AACG, PCIN57FL = Yes, TRTEMFL = yes, SMQ12 through 14NAM, SMQ12 through 14SC = narrow, AEDOSEFL = Y or N.

In the all-donanemab pool, 9% of participants reported a TEAE belonging to the SMQ of Hypersensitivity (narrow) with onset within 24 hours of an infusion. The following table shows the frequency of TEAEs belonging to the SMQs of Anaphylactic Reaction, Hypersensitivity, and Angioedema (Narrow) in the all-donanemab pool at the 90-Day Safety Update.

Table 62. Frequency of TEAEs Belonging to the SMQs of Anaphylactic Reaction, Hypersensitivity, and Angioedema (Narrow) in the All-Donanemab Pool at the 90-Day Safety Update

SMQ, Onset ¹	DON N=1304 n (%)
Anaphylactic reaction, ≤ 24 hours	4 (<0.5)
Anaphylactic reaction, > 24 hours	0
Hypersensitivity, ≤ 24 hours	116 (9)
Hypersensitivity, > 24 hours	42 (3)
Angioedema, ≤ 24 hours	1 (<0.5)
Angioedema, > 24 hours	5 (<0.5)

¹TEAE onset from the time of the donanemab infusion. The reviewer created this using the IDB ADAE dataset submitted 8.25.22, TRT01A = inversion of Dona-C, SAFFL = Yes, LYIN57FL = Yes, TRTEMFL = Yes, grouped on USUBJID, SMQ12 through 14NAM, SMQ12SC, SMQ13SC, SMQ14SC, AEDOSEFL.

Within the SMQ of Hypersensitivity (narrow), infusion related reactions were the most frequently reported TEAE with onset within 24 hours of an infusion in Study AACG (9/131; 7% for donanemab vs none in placebo). Bullous dermatitis was reported in one patient on donanemab (1%) vs none in placebo. Similarly, in the all-donanemab pool, infusion related

reaction was the most frequently reported TEAE within the SMQ of Hypersensitivity (narrow) within 24 hours of an infusion (8% [106/1304]).

TEAEs belonging to the SMQ of Hypersensitivity (narrow) and with onset greater than 24 hours from the time of infusion in donanemab-treated participants and more frequently than in placebo included allergic dermatitis, drug eruption, and urticaria in Study AACG, each reported in 1% (1/131) of patients.

In the all-donanemab pool, infusion related reaction was the most frequently reported TEAE occurring greater than 24 hours from the time of infusion and belonging to the SMQ of hypersensitivity (narrow) (frequency of 1% [10/1304]). Other preferred terms belonging to the SMQ of hypersensitivity (narrow) and with onset greater than 24 hours from the time of infusion in at least two participants included rash, dermatitis, contact dermatitis, urticaria, eczema, allergic dermatitis, and hypersensitivity.

The majority of TEAEs belonging to the SMQs of Anaphylactic Reaction, Hypersensitivity, and Angioedema (Narrow) were mild or moderate in severity in Study AACG. The following table shows TEAEs belonging to the SMQs of Anaphylactic Reaction, Hypersensitivity, and Angioedema (Narrow) by severity in Study AACG.

Table 63. TEAEs Belonging to the SMQs of Anaphylactic Reaction, Hypersensitivity, and Angioedema (Narrow) by Severity in Study AACG

Severity	DON N=131 n (%)	Placebo N=125 n (%)
Participant Reporting at Least One TEAE	15 (100)	14 (100)
Mild	9/15 (60)	11/14 (79)
Moderate	7/15 (47)	3/14 (21)
Severe	2/15 (13)	1/14 (7)

The reviewer created this using the IDB ADAE dataset submitted 8.25.22, SAFFL = Yes, StudyID=AACG, PCIN57FL = Yes, TRTEMFL = yes, select row where SMQ12SC, 13SC, or 14SC = NARROW, grouped on USUBJID, AESEV, TRT01A

Similar findings were observed in the all-donanemab pool where the majority of TEAEs belonging to the SMQs of Anaphylactic Reaction, Hypersensitivity, and Angioedema (Narrow) were mild or moderate in severity. The reader is referred to the [Appendix](#) for a table showing TEAEs belonging to the SMQs of Anaphylactic Reaction, Hypersensitivity, and Angioedema (Narrow) by severity in the all-donanemab pool at the 90-Day Safety Update.

Approximately 95% of participants experienced their first hypersensitivity/infusion related reaction by the 5th dose of donanemab in Study AACG. Similar findings were observed for the

all-donanemab pool (92% by the 5th dose).⁶⁵ The following table shows the percentage of donanemab-treated participants with first hypersensitivity/infusion related reaction by infusion number in Study AACG.

Table 64. Percentage of Donanemab-treated Participants with First Hypersensitivity/Infusion Related Reaction Event by Donanemab Infusion Number in Study AACG.

Number of Donanemab Infusions	# of Participants with First Hypersensitivity/I RR Event	Cumulative # Participants with 1st Hypersensitivity/I RR Event	Cumulative % of Participants with 1st Hypersensitivity/I RR Event	# of Participants with First Serious Hypersensitivity/I RR Event
1	1	1	5	1
2	4	5	26	0
3	4	9	47	0
4	5	14	74	2
5	4	18	95	0
6	0	18	95	0
7	0	18	95	0
8	0	18	95	0
9	1	19	100	0

Data in the table is taken from the sponsor's response dated November 7, 2022, to an information request dated November 3, 2022.

In participants who reported events related to hypersensitivity and infusion related reaction that occurred within 24 hours of donanemab administration, most events were reported to occur during the drug administration or within 30 minutes of the end of study drug administration in donanemab-treated participants in Study AACG (84% [16/19]). Similar findings were observed in the all-donanemab pool (83% [114/138]).⁶⁶ The following table shows onset of events of hypersensitivity and infusion related events from donanemab administration in Study AACG as collected by Hypersensitivity/IRR Follow Up Forms for Events occurring within 24 hours of donanemab administration.

⁶⁵ Noted on page 16 of the sponsor's response dated November 7, 2022, to an information request dated November 3, 2022.

⁶⁶ Noted on page 21 of the sponsor's response dated November 7, 2022, to an information request dated November 3, 2022.

Table 65. Timing of Hypersensitivity/IRR Events Occurring Within 24 Hours of an Infusion as reported on Hypersensitivity/IRR Follow Up Form in Study AACG

Timing	DON N=131 n (%)	Placebo N=125 n (%)
Participants Reporting at Least One Event Occurring Within 24 hours of an Infusion on the Hypersensitivity/IRR Follow Up Form	14 (10.7)	3 (2.4)
Timing of Event		
During Drug Administration	12 (9.2)	2 (1.6)
Within 30 Minutes of End of Study Drug Administration	4 (3.1)	0
>30 minutes and up to 6 hours from end of study drug administration	2 (1.5)	1 (0.8)
>6 hours and up to 24 hours from end of study drug administration	1 (0.8)	0

The reviewer created this table using the IDB FA dataset, FACAT = hypersensitivity, anaphylactic reaction, and infusion related reactions follow up joined with IDB ADSL submitted on 8.25.22 by USUBJID (include non-matches), new column created with below formula, set new column = 1, call this FA1. Take FA1, FATESTCD = HAIRFU59, FASTREC = 1, 2, 3, 4, select columns STUDYID, USUBJID, and FAGRPID and call this FA2. Merge FA1 to FA2 by STUDYID, USUBJID, FAGRPID (do not include non-matches) and call this FA3. Join FA3 with IDB ADSL by USUBJID (do not include non-matches).

The Sponsor notes that among 10 participants with at least one infusion reaction, 6 received treatment.⁶⁷ Treatment for an infusion reaction could have included epinephrine, diphenhydramine, ibuprofen, methylprednisolone, ondansetron, or acetaminophen or slowing of the infusion. The Sponsor notes that following a first occurrence of an infusion reaction, 6 participants were rechallenged with donanemab of which 5 had a subsequent infusion reaction on rechallenge. Among the 6 rechallenged participants, 2 participants received premedications for at least one subsequent infusion of donanemab.

Narratives Related to Hypersensitivity and Infusion-Related Reactions

Nine SAEs related to the topic of hypersensitivity and infusion related reaction were reported in nine donanemab-treated participants in Phase 2 and 3 studies (preferred terms: infusion related reaction [n=5], anaphylactic reaction [n=3], and drug eruption).⁶⁸ A role for donanemab was likely in all cases based on onset of the events relative to the most recent infusion. The reader is referred to the [Narratives](#) section in the Serious Adverse Events section of this review for further details.

⁶⁷ Noted on page 129 of the Study AACG CSR.

⁶⁸ Infusion related reaction: I5T-MC-AACG- (b) (6) I5T-MC-AACI- (b) (6) I5T-MC-AACI- (b) (6) I5T-MC-AACG- (b) (6) I5T-MC-AACI- (b) (6) anaphylactic reaction: I5T-MC-AACI- (b) (6) I5T-MC-AACI- (b) (6) and I5T-MC-AACI- (b) (6) drug eruption: AACG- (b) (6)

The following table summarizes six cases related to the topic of anaphylaxis in Phase 2 and 3 Studies. Four of the cases were serious (Anaphylactic Reaction/[I5T-MC-AACI-](#)^{(b) (6)}
[I5T-MC-AACI-](#)^{(b) (6)} and [I5T-MC-AACI-](#)^{(b) (6)} Syncope/[I5T-MC-AACI-](#)^{(b) (6)}). Based on clinical criteria developed by Sampson et al. 2006 to identify cases of anaphylaxis, this reviewer assessed four of the six cases as likely anaphylactic reactions ([I5T-MC-AACI-](#)^{(b) (6)}
[I5T-MC-AACI-](#)^{(b) (6)} [I5T-MC-AACI-](#)^{(b) (6)} and [I5T-MC-AACI-](#)^{(b) (6)}) and the remaining two as possible anaphylactic reactions ([I5T-MC-AACI-](#)^{(b) (6)} and [I5T-MC-AACI-](#)^{(b) (6)}).⁶⁹

Table 66. Cases Related to the Topic of Anaphylactic Reaction in Phase 2 and 3 Studies

Subject ID/ AE term	Onset Relative to Donanemab Infusion	Symptoms and Risk Factors	Treatment and Outcome
I5T-MC- AACI- ^{(b) (6)} ^{(b) (6)} SAE: Anaphylactic Reaction	5 minutes from the start of the 2 nd infusion	SX: diarrhea, vomiting, weakness of the limbs, hypotension (88/57 mmHg) RF: history of anaphylactic reaction (cefotiam hydrochloride and penicillin)	Infusion stopped TX: Epinephrine and calcium chloride/potassium/sodium chloride/sodium lactate Hospitalized SAE considered resolved the following day Study Drug was discontinued
I5T-MC- AACI- ^{(b) (6)} ^{(b) (6)} SAE: Anaphylactic Reaction	25 minutes after the end of the 1 st infusion	SX: mucocutaneous urticaria, swelling and erythema of neck, throat and chest tightness, dry cough, bronchospasm RF: none identified	TX: diphenhydramine, epinephrine, methylprednisolone, and oral famotidine Taken to the emergency department SAE considered resolved the same day Study Drug was discontinued

⁶⁹ Sampson H, Munoz-Furlong A, Campbell R, et al. Second symposium on the definition and management of anaphylaxis: summary report-Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. J Allergy Clin Immunol 2006; 117:391-397.

Subject ID/ AE term	Onset Relative to Donanemab Infusion	Symptoms and Risk Factors	Treatment and Outcome
I5T-MC- AACI- (b) (6) (b) (6) SAE: Anaphylactic Reaction	12 minutes from the start of the 3 rd infusion	SX: generalized erythema (chest, abdomen, back, throat, lip, ear, and eyelid), chest tightness, tachycardia, elevated blood pressure (171/99 mmHg), and nausea RF: drug intolerance (codeine, levofloxacin and sulfa),	Infusion stopped TX: epinephrine, intravenous diphenhydramine, and a normal saline bolus SAE considered resolved the same day Study Drug was discontinued
I5T-MC- AACI- (b) (6) (b) (6) TEAE: Anaphylactic Reaction	13 minutes from the start of the 6 th infusion	SX: chest pain, low blood pressure of 92/60 mmHg (preinfusion BP 128/80 mmHg) ¹ , chest tightness, fear/panic, headache, weakness of limb, nausea/vomiting, sweating, and tightening of throat	TX: none reported Study drug temporarily interrupted at the time of the data cutoff.
I5T-MC- AACI- (b) (6) (b) (6) TEAE: Infusion Related Reaction	During drug administration of the 3 rd infusion	BP: 78/60 PR: 50 bpm (preinfusion: 110/75 mmHg PR: 69 bpm) SX: chest pain, headache, vertigo, chills, sweating, difficulty breathing/dyspnea, and wheezing	Infusion stopped TX: diphenhydramine and sodium chloride BP returned to baseline 3 hours later.
I5T-MC- AACI- (b) (6) (b) (6) SAE: Syncope	5 minutes from the start of the fourth infusion	BP: 144/98 mmHg, PR: 89 bpm after the syncopal event (preinfusion: BP: 140/82 mmHg, PR: 83 bpm)	Infusion stopped TX: none reported Hospitalized

¹Noted in a response dated November 15, 2022, to an information request dated November 10, 2022. ED: emergency department, RF: risk factors, SX: symptoms, TX: treatment. The reviewer created this table using data from narratives noted in the Table of Significant and Notable Patients submitted May 18, 2022.

Although most serious cases related to the topic of hypersensitivity and infusion related reaction occurred within 24 hours, the reviewer notes one SAE of drug eruption that occurred nine days after the first infusion ([I5T-MC-AACG-](#) (b) (6)). The reader is referred to the Serious Adverse Events section of this review for further details.

This reviewer notes that cases of hypersensitivity and infusion-related reactions were associated with changes in blood pressure.

One SAE of subarachnoid hemorrhage was reported in a participant with a likely infusion related reaction ([15T-MC-AACG-](#) (b) (6)). In this case, this reviewer considered the infusion related reaction as contributory in the SAE of subarachnoid hemorrhage. The reader is referred to the Narratives section of the Serious Adverse Events section of this review for further details.

One case of hypertensive crisis occurred during a donanemab infusion in a participant with underlying uncontrolled blood pressure where a role for donanemab in the AE could not be ruled out ([AACD-](#) (b) (6)). The participant's uncontrolled blood pressure was a likely contributory factor in the case. The case is discussed further in the Dropouts and/or Discontinuations of the Adverse Effects section of this review.

Two cases of infusion related reaction were associated with collapse/fainting ([15T-MC-AACI-](#) (b) (6) and [15T-MC-AACI-](#) (b) (6)). In both cases, infusion related reaction was reported to lead to treatment discontinuation. The reader is referred to Dropouts and/or Discontinuations section of this review for narratives of these cases.

One case of infusion related reaction with reported increases in blood pressure is discussed in the Dropouts and/or Discontinuations section of this review ([15T-MC-AACI-](#) (b) (6)).

This reviewer identified three additional participants in Phase 2 and 3 Studies who reported TEAEs of infusion related reaction and had notable changes in blood pressure, which are summarized in the following table. In one case, the participant experienced the SAE of infusion related reaction with elevated blood pressure of 220/70 mmHg, then low blood pressure (systolic of 80 mmHg upon standing), and subsequently developed atrial fibrillation with rapid ventricular rate ([15T-MC-AACG-](#) (b) (6)). The subject's past medical history of atrial fibrillation was also likely a contributory factor in the event of atrial fibrillation. The case is discussed further in the Narratives section of the Serious Adverse Events section of this review. In a second case, the participant experienced an infusion related reaction with an elevated blood pressure of 240/120 mmHg and elevated heart rate of 130 beats per minute ([15T-MC-AACI-](#) (b) (6)). The case is discussed further in the Dropouts and/or Discontinuations section of this review.

The following table shows symptoms and vital signs pre- and post-initiation of infusion in the three participants the reviewer identified as having infusion related reaction with notable changes in blood pressure across Phase 2 and 3 Studies.

Table 67. Infusion Related Reactions and Associated Blood Pressure Changes After Infusion Initiation in Three Participants in Phase 2 and 3 Studies

USUBJID	Study Day/Infusion Number	Vitals before Start of Infusion	Vitals after Start of Infusion/ Symptoms
I5T-MC-AACG- (b) (6)	122/ 4	BP: 130/72 mmHg Pulse rate: 68 bpm	At the time of stopping the infusion - BP: 220/70 mmHg, pulse rate 72 bpm. Symptom of nausea Seven minutes after stopping the infusion - Systolic bp of 80 mmHg (upon standing) 17 minutes after stopping the infusion - BP: 140 mmHg (type of BP not reported) Symptoms: shortness of breath, nausea, and anxiety. 23 minutes after stopping the infusion - BP: 180/75 mmHg 1-2 hours after stopping the infusion - In the ER, developed Afib with RVR in the 150s
I5T-MC-AACI- (b) (6)	74/ 3	BP: 137/72 mmHg PR: 66 bpm	BP: 180s/80s (after the infusion) Symptoms: diarrhea, nausea/vomiting, chills, and back pain
I5T-MC-AACI- (b) (6)	58/ 3	BP: 120/70 mmHg PR: 67 bpm	BP: 240/120 mmHg, PR: 130 bpm Symptoms: trouble breathing, tachypnea, chest pain, back pain

BP: blood pressure, PR: pulse rate, Afib: atrial fibrillation, RVR: rapid ventricular rate. Data in the table is noted in the Table of Significant and Notable Patients and in a response dated September 15, 2022, to an information request dated September 13, 2022.

In summary, serious cases of infusion related reaction and anaphylaxis were reported in donanemab-treated participants in Phase 2 and 3 Studies. Increases and decreases in blood pressure were observed in participants reporting infusion related reactions. Infusion related reactions were among the most frequently reported TEAEs in Study AACG. Most TEAEs related to hypersensitivity were mild or moderate in severity. Most first events of hypersensitivity had occurred by the 4th infusion. Most cases of hypersensitivity and infusion related reaction had onset during the infusion or within 30 minutes after the end of the infusion.

8.5.3. Suicide-related Events

This reviewer did not identify a safety signal for suicide-related events based on responses to the C-SSRS in Study AACG and the all-donanemab pool and a review of narratives of suicide-related events.

The sponsor evaluated the frequency of positive responses to the Columbia Suicide Severity Rating Scale (C-SSRS) in Study AACG and the all-donanemab pool and narratives of suicide-related events. In Study AACG, the C-SSRS was administered at screening and during every study visit during the treatment period, the end of study visit, and between Week 88 and 124.

Overall, this reviewer found the sponsor's approach for evaluation of suicide-related events to be acceptable.

Donanemab-treated participants did not have a higher frequency of positive responses to the C-SSRS compared to placebo in Study AACG. The following table identifies the frequency of suicidal ideation, behavior, and self-injurious behavior without suicidal intent based on responses to the C-SSRS in Study AACG.

Table 68. Suicidal Ideation, Behavior, and Self-Injurious Behavior Without Suicidal Intent Using the C-SSRS in Study AACG.

Responses	DON N=131 n (%)	Placebo N=124 n (%)
Suicidal Ideation (1-5)	1 (1)	9 (7)
1. Wish to be Dead	1 (1)	8 (6)
2. Non-Specific Active Suicidal Thoughts	0	5 (4)
3. Active suicidal ideation with Any methods (Not Plan) without intent to Act	0	3 (2)
4. Active suicidal ideation with some intent to Act, without specific plan	0	1 (1)
5. Active suicidal ideation with specific plan and intent	0	1 (1)
Suicidal Behavior (6-10)	0	0
6. Preparatory Acts or Behavior	0	0
7. Aborted Attempt	0	0
8. Interrupted Attempt	0	0
9. Actual Attempt (Non-Fatal)	0	0
10. Completed Suicide	0	0
Suicidal Ideation or Behavior (1-10)	1 (1)	9 (7)
Non-Suicidal Self Injurious Behavior	0	0

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The denominator is based on the number of participants who had a post-baseline response to the C-SSRS. The reviewer created this table using the ADCSSRS, AVIST = postbaseline MAX PC IN, AVALC=Y.

Compared to Study AACG, the all-donanemab pool at the time of the 90-Day Safety Update had a similar frequency of participants with positive responses to the C-SSRS for suicidal ideation or behavior (responses 1-10) (1% versus 2%, respectively). No participants had a positive response for non-suicidal self-injurious behavior in the all-donanemab pool.

Review of AEs related to suicide-related events

One SAE of suicidal depression was reported in one participant in the all-donanemab pool at the time of the 90-Day Safety Update. A role for donanemab in the non-fatal case could not be ruled out given temporal association (occurring 31 days after the first dose/[I5T-MC-AACI-](#)^{(b) (6)}^{(b) (6)}). Other potential confounding factors existed in the case, including worsening AD and financial difficulty. The reader is referred to the Narratives section of the Serious Adverse Events section of this review for a summary of the case.

One TEAE of suicidal ideation was reported to lead to study withdrawal in one participant in the all-donanemab pool at the 90-Day Safety Update ([I5T-MC-AACG-](#)^{(b) (6)}). A role for donanemab could not be ruled out given temporal association with donanemab infusion; however, potential contributory factors existed in this case including a history of depression and Covid-19 infection within four weeks of AE onset. The reader is referred to the Dropouts and/or Discontinuations Due to Adverse Effects section of this review for a summary of the case.

In the blinded main study of AACI, a role for donanemab in three SAEs related to suicide-related events with fatal outcome could not be established as treatment was still blinded at the time of the 90-Day Safety Update. The reader is referred to the Deaths section of this review for further details of these cases (completed suicide/[I5T-MC-AACI-](#)^{(b) (6)}^{(b) (6)}, completed suicide/[I5T-MC-AACI-](#)^{(b) (6)} and suicide attempt [I5T-MC-AACI-](#)^{(b) (6)}^{(b) (6)}).

In summary, this reviewer did not identify a safety signal for suicide-related events based on responses to the C-SSRS in Study AACG and the all-donanemab pool and a review of narratives of suicide-related events.

8.6. Safety Analyses By Demographic Subgroups

ARIA-H microhemorrhage was observed with higher frequency in males compared to females. Nausea and urinary tract infection were reported with higher frequency in females compared to males. ARIA-E and nausea were reported with higher frequency in participants < 75 years of age, and ARIA-H microhemorrhage was reported with higher frequency in participants ≥ 75 years. ARIA-E, ARIA-H microhemorrhage, and ARIA-H superficial siderosis occurred with higher frequency in participants within the lowest body mass index (BMI) tertile compared to the

highest BMI tertile. The low number of participants in each arm within each of the demographic subgroups (< 70) limits the generalizability of these conclusions. A conclusion on the frequency of common TEAEs by race and ethnicity cannot be drawn given the low number of participants with non-White race and Hispanic ethnicity in Study AACG.

In order to evaluate the effect of sex, age, race, and ethnicity on the safety of donanemab, this reviewer assessed frequencies of most common TEAEs reported in Study AACG (ARIA-E, ARIA-H microhemorrhage, ARIA-H superficial siderosis, infusion related reaction, nausea, and urinary tract infection) by sex, age group, race, and ethnicity. In addition, this reviewer analyzed common TEAEs by BMI in order to assess the impact of BMI on frequency of TEAEs. Because Study AACG was performed in sites located only in North America, an analysis of the impact of region on TEAEs was not performed.

ARIA-H microhemorrhage was observed with higher frequency in donanemab-treated male participants compared to female participants in Study AACG (27% versus 13%, respectively). As noted in the section on [ARIA](#), male and female participants had similar frequencies of ARIA-H microhemorrhage (difference no greater than 2%). A higher frequency of nausea (15% versus 6%, respectively) and urinary tract infection (15% versus 5%, respectively) were reported in donanemab-treated female participants compared to male participants in Study AACG. The following table shows the frequency of common TEAEs by sex in Study AACG.

Table 69. Frequency of Common TEAEs by Sex in Study AACG

AE	Donanemab		Placebo	
	F N=68 n (%)	M N=63 n (%)	F N=64 n (%)	M N=61 n (%)
ARIA-E	20 (29)	15 (24)	0	1 (2)
ARIA-H microhemorrhage	9 (13)	17 (27)	3 (5)	3 (5)
ARIA-H superficial siderosis	11 (16)	11 (17)	1 (2)	2 (3)
Infusion related reaction	6 (9)	4 (6)	0	0
Nausea	10 (15)	4 (6)	2 (3)	2 (3)
Urinary tract infection	10 (15)	3 (5)	3 (5)	2 (3)

F: female, M: male. The reviewer created this using the IDB ADAE dataset submitted 8.5.22, SAFFL = Yes, StudyID=AACG, PCIN57FL = Yes, TRTEMFL = yes, for infusion related reaction, nausea, and urinary tract infection and using the IDB ADXP submitted on October 13, 2022, StudyID = AACG, PCSAFFL from ADSL = Yes, TEPC57FL = yes, PARAM = severity of ARIA-E, ARIA-H MH, and ARIA-H SS, for ARIA-E, ARIA-H microhemorrhage, and ARIA-H superficial siderosis.

The number of participants with age < 65 years in Study AACG was low (10 participants), and a conclusion of the frequency of common TEAEs by age group < 65 years cannot be drawn. A higher frequency of ARIA-E (32% versus 26%, respectively) and nausea (15% versus 8%,

respectively) were reported in donanemab-treated participants < 75 years compared to participants ≥ 75 years in Study AACG. A higher frequency of ARIA-H microhemorrhage was reported in donanemab-treated participants ≥ 75 years compared to < 75 years in Study AACG (25% versus 18%, respectively). The following table shows the frequency of common TEAEs by age group in Study AACG.

Table 70. Frequency of Common TEAEs by Age Group in Study AACG

AE	Donanemab		Placebo	
	< 75 years N=60 n (%)	≥75 years N=61 n (%)	< 75 years N=51 n (%)	≥75 years N=74 n (%)
ARIA-E	19 (32)	16 (26)	1 (2)	0
ARIA-H microhemorrhage	11 (18)	15 (25)	1 (2)	5 (7)
ARIA-H superficial siderosis	11 (18)	11 (18)	1 (2)	2 (3)
Infusion related reaction	6 (10)	4 (7)	0	0
Nausea	9 (15)	5 (8)	3 (6)	1 (1)
Urinary tract infection	5 (8)	8 (13)	2 (4)	3 (4)

The reviewer created this using the IDB ADAE dataset submitted 8.5.22, SAFFL = Yes, StudyID=AACG, PCIN57FL = Yes, TRTEMFL = yes, for infusion related reaction, nausea, and urinary tract infection and using the IDB ADXP submitted on October 13, 2022, StudyID = AACG, PCSAFL from ADSL = Yes, TEPC57FL = yes, PARAM = severity of ARIA-E, ARIA-H MH, and ARIA-H SS, for ARIA-E, ARIA-H microhemorrhage, and ARIA-H superficial siderosis.

The number of participants with race other than White in Study AACG was low (14 participants) and a conclusion of the frequency of common TEAEs by race cannot be drawn. The following table shows the frequency of common TEAEs by White and Black race, races with the largest number of participants, in Study AACG.

Table 71. Frequency of Common TEAEs by Race in Study AACG

AE	Donanemab		Placebo	
	White N=122 n (%)	Black N=5 n (%)	White N=120 n (%)	Black N=3 n (%)
ARIA-E	34 (28)	1 (20)	1 (1)	0
ARIA-H microhemorrhage	26 (21)	0	6 (5)	0
ARIA-H superficial siderosis	22 (18)	0	2 (2)	1 (33)
Infusion related reaction	9 (7)	0	0	0
Nausea	14 (11)	0	4 (3)	0
Urinary tract infection	12 (10)	0	5 (4)	0

The reviewer created this using the IDB ADAE dataset submitted 8.5.22, SAFFL = Yes, StudyID=AACG, PCIN57FL = Yes, TRTEMFL = yes, for infusion related reaction, nausea, and urinary tract infection and using the IDB ADXP

submitted on October 13, 2022, StudyID = AACG, PCSAFL from ADSL = Yes, TEPC57FL = yes, PARAM = severity of ARIA-E, ARIA-H MH, and ARIA-H SS, for ARIA-E, ARIA-H microhemorrhage, and ARIA-H superficial siderosis.

The number of participants with Hispanic ethnicity in Study AACG was low (8 participants) and a conclusion of the frequency of common TEAEs by ethnicity cannot be drawn. The following table shows the frequency of common TEAEs by ethnicity in Study AACG.

Table 72. Frequency of Common TEAEs by Ethnicity in Study AACG

AE	Donanemab		Placebo	
	Hispanic N=5 n (%)	Non- Hispanic N=126 n (%)	Hispanic N=3 n (%)	Non- Hispanic N=122 n (%)
ARIA-E	1 (20)	34 (27)	0	1 (1)
ARIA-H microhemorrhage	1 (20)	25 (20)	0	6 (5)
ARIA-H superficial siderosis	0	22 (17)	0	3 (2)
Infusion related reaction	1 (20)	9 (7)	0	0
Nausea	0	14 (11)	1 (33)	3 (2)
Urinary tract infection	1 (20)	12 (10)	0	5 (4)

The reviewer created this using the IDB ADAE dataset submitted 8.5.22, SAFFL = Yes, StudyID=AACG, PCIN57FL = Yes, TRTEMFL = yes, for infusion related reaction, nausea, and urinary tract infection and using the IDB ADXP submitted on October 13, 2022, StudyID = AACG, PCSAFL from ADSL = Yes, TEPC57FL = yes, PARAM = severity of ARIA-E, ARIA-H MH, and ARIA-H SS, for ARIA-E, ARIA-H microhemorrhage, and ARIA-H superficial siderosis.

A higher frequency of ARIA-E, ARIA-H microhemorrhage, and ARIA-H superficial siderosis were reported in donanemab-treated participants within the lowest BMI compared to the highest BMI tertile in Study AACG (35% versus 20%, respectively). The following table shows the frequency of common TEAEs by BMI tertiles in Study AACG.

Table 73. Frequency of Common TEAEs by Body Mass Index (kg/m²) Tertiles in Study AACG

AE	Donanemab			Placebo		
	< 24 N=43 n (%)	≥24 and < 27 N=39 n (%)	>27 N=49 n (%)	< 24 N=44 n (%)	≥24 and < 27 N=31 n (%)	>27 N=50 n (%)
ARIA-E	15 (35)	10 (26)	10 (20)	0	1 (3)	0
ARIA-H microhemorrhage	10 (23)	6 (15)	10 (20)	0	3 (10)	3 (6)
ARIA-H superficial siderosis	10 (23)	5 (13)	7 (14)	2 (5)	0	1 (2)
Infusion related reaction	3 (7)	0	7 (14)	0	0	0
Nausea	4 (9)	3 (8)	7 (14)	2 (5)	0	2 (4)

AE	Donanemab			Placebo		
	< 24 N=43 n (%)	≥24 and < 27 N=39 n (%)	>27 N=49 n (%)	< 24 N=44 n (%)	≥24 and < 27 N=31 n (%)	>27 N=50 n (%)
Urinary tract infection	5 (12)	2 (5)	6 (12)	2 (5)	1 (3)	2 (4)

The reviewer created this using the IDB ADAE dataset submitted 8.5.22, SAFFL = Yes, StudyID=AACG, PCIN57FL = Yes, TRTEMFL = yes, for infusion related reaction, nausea, and urinary tract infection and using the IDB ADXP submitted on October 13, 2022, StudyID = AACG, PCSAFL from ADSL = Yes, TEPC57FL = yes, PARAM = severity of ARIA-E, ARIA-H MH, and ARIA-H SS, for ARIA-E, ARIA-H microhemorrhage, and ARIA-H superficial siderosis.

8.7. Specific Safety Studies/Clinical Trials

Not applicable.

8.8. Additional Safety Explorations

8.8.1. Human Carcinogenicity or Tumor Development

This reviewer did not identify a safety signal for human carcinogenicity or tumor development in a review of TEAEs belonging to the SOC of Neoplasm Benign, Malignant, and Unspecified in Study AACG or the all-donanemab pool. A conclusion about the carcinogenic potential of donanemab cannot be drawn, given the low number of subjects with exposure to donanemab of at least 12 months or more (49 subjects at the time of the 90-Day Safety Update) and less than one year follow up for most participants.

In Study AACG, donanemab and placebo arms had similar frequencies of subjects reporting at least one TEAE belonging to the SOC of Neoplasm Benign, Malignant, and Unspecified and reporting TEAEs by preferred term (difference no greater than 2%). The following table shows TEAEs belonging to the SOC of Neoplasm Benign, Malignant, and Unspecified in Study AACG.

Table 74. TEAE Belonging to the SOC Neoplasms Benign, Malignant and Unspecified in Study AACG.

Adverse Event	DON N=131 n (%)	Placebo N=125 n (%)
Subject Reporting at Least One TEAE	12 (9)	12 (10)
Skin	8 (6)	10 (8)
Atypical fibroxanthoma	1 (1)	0
Basal cell carcinoma	3 (2)	4 (3)
Bowen's disease	0	1 (1)
Dysplastic naevus	1 (1)	0

Adverse Event	DON N=131 n (%)	Placebo N=125 n (%)
Keratoacanthoma	0	1 (1)
Lip neoplasm	0	1 (1)
Malignant melanoma	0	1 (1)
Seborrheic keratosis	1 (1)	0
Skin papilloma	0	1 (1)
Squamous cell carcinoma	3 (2)	1 (1)
Squamous cell carcinoma of skin	1 (1)	2 (2)
Pulmonary	3 (2)	0
Benign lung neoplasm	2 (2)	0
Lung adenocarcinoma	1 (1)	0
Non-small cell lung cancer stage II	1 (1)	0
Miscellaneous	2 (2)	2 (2)
Bladder squamous cell carcinoma stage II	0	1 (1)
Breast cancer	1 (1)	0
Neuroma	1 (1)	0
Non-Hodgkin's lymphoma	0	1 (1)

The reviewer created this using the IDB ADAE dataset submitted 8.25.22, TRT01A = inversion of Dona-C, SAFFL = Y, LYIN57FL = Y, TRTEMFL = Y, AESOC = Neoplasms Benign, Malignant and Unspecified.

In the all-donanemab pool at the 90-Day Safety Update, 3% of participants reported at least one TEAE belonging to the SOC of Neoplasms Benign, Malignant and Unspecified (38/1304). No preferred term had frequency higher than 1% in the all-donanemab pool at the time of the 90-Day Safety Update.

The median duration of follow up from the first dose of donanemab to the end of study, data cutoff point, or date of study withdrawal for the all-donanemab pool at the 90-Day Safety Update was 194 days (minimum: 1 day, maximum: 897 days, 25% quantile: 106 days, 75% quantile: 211 days).⁷⁰ Given that most subjects had less than one year of follow up, a conclusion about the carcinogenic potential of donanemab cannot be drawn.

8.8.2. Human Reproduction and Pregnancy

⁷⁰ Duration of follow up calculated using the IDB ADSL submitted on 8.25.22, LYTRPG1 = not missing, TRT01A = inverse of Dona-C, joined with IDB ADDS, max ADT for USUBJID.

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There are no safety data on the use of donanemab in pregnant persons. The sponsor notes that pregnant persons were excluded from clinical studies. There were no instances of pregnancy or use during lactation in the development program.

8.8.3. Pediatrics and Assessment of Effects on Growth

Not applicable.

8.8.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Overdose

This reviewer did not identify cases of overdose with donanemab in a search of TEAEs related to overdose in the all-donanemab pool.

The reviewer searched for TEAEs related to overdose in the all-donanemab pool at the 90-Day Safety Update, participants treated with a combination of donanemab-C and BACE-I, and in Study AACC or AACD.

The reviewer did not identify any TEAEs related to overdose with donanemab. One subject in the all-donanemab pool was noted to have to the TEAE of overdose with verbatim term insulin overdose (I5T-MC-AACI- (b) (6)). Three subjects were recorded as having been dispensed 2800 mg of donanemab at the same visit; however, the sponsor noted that in each of the cases, the participant did not receive more than planned dose.⁷¹ In two cases, additional study drug was dispensed because of incorrect drug preparation (I5T-MC-AACG- (b) (6) and I5T-MC-AACI- (b) (6)). In the third case, the participant had interruption of an infusion because of a presyncopal event, and the investigational product had to be dispensed two days later (5T-MC-AACI- (b) (6)).

The sponsor performed a similar search and did not identify a safety signal for overdose with donanemab.

Drug Abuse Potential

This reviewer did not identify a safety signal for drug abuse potential in a search of TEAEs related to abuse potential in the all-donanemab pool.

A consult with the Controlled Substance Staff (CSS) was not obtained for this review. Given that donanemab is anticipated to be given in a monitored setting, the anticipated risk for abuse appears to be low. In addition, abuse potential has not been identified with aducanumab or lecanemab, other amyloid-directed monoclonal antibody drugs.

⁷¹Noted a the sponsor's response dated November 8, 2022, to an information request dated November 7, 2022.

The reviewer searched for TEAEs belonging to the SMQ Drug Abuse and Dependence and did not identify any TEAEs related to drug abuse potential with donanemab in the all-donanemab pool at the 90-Day Safety Update or in participants treated with a combination of donanemab-C and BACE-I in Study AACG.

The sponsor performed a similar search and noted similar findings.

Withdrawal and Rebound

This reviewer did not identify a safety signal for withdrawal and rebound in a search of TEAEs belonging to the SMQ Drug Withdrawal.

One donanemab-treated participant reported a TEAE belonging to the SMQ of Drug Withdrawal compared to none on placebo in Study AACG (0.8% [1/131] versus none [0/125], respectively). In this participant, the TEAE of drug withdrawal headache (mild) was reported in on Study Day 58, 28 days after the second dose of donanemab 700 mg (I5T-MC-AACG- (b) (6)). The participant was reported to have ongoing mild asymptomatic ARIA-E (onset on Study Day 30, resolved Study Day 70) and ARIA-H superficial siderosis (onset Study Day 30, not covered/resolved at the time of study drug discontinuation). The study drug was discontinued per protocol discontinuation criteria of >1 treatment-emergent new area of superficial siderosis.

No additional TEAEs belonging to the SMQ of Drug Withdrawal were reported in the all-donanemab pool at the time of the 90-Day Safety Update.

8.9. Safety in the Postmarket Setting

8.9.1. Safety Concerns Identified Through Postmarket Experience

Not applicable. Donanemab is a new molecular entity. It is not approved in other regions of the world.

8.9.2. Expectations on Safety in the Postmarket Setting

The population of patients studied did not include patients with moderate or severe dementia, and safety outcomes in these patients is unknown.

The number of participants in the safety database with 12 months or more of exposure to donanemab is low. Monitoring of postmarketing adverse events will help provide additional information on the long-term safety of donanemab.

Conclusion about the carcinogenic potential of donanemab cannot be drawn, given the low

number of subjects with exposure to donanemab for at least 12 months or more.

A low number of subjects were enrolled in the placebo-controlled study of AACG within the demographic subgroups of age less than 65 years, age 85 years or older, non-White race, and Hispanic ethnicity, and conclusions regarding the impact of these demographic subgroups on the frequency of adverse events cannot be drawn.

Participants who experienced events of intracerebral hemorrhage > 1 cm while on treatment with donanemab did not receive additional doses of donanemab after the events of intracerebral hemorrhage. The safety of continued treatment with donanemab in patients who have experienced intracerebral hemorrhage > 1 cm while on donanemab therapy is unknown.

8.9.3. Additional Safety Issues From Other Disciplines

Not applicable.

8.10. Integrated Assessment of Safety

Safety findings from BLA 761248 are summarized below.

Relevant characteristics of the safety population. Participants with moderate or severe dementia were not included in the key clinical studies for safety. Treatment was discontinued in clinical studies once patients met criteria for amyloid plaque reduction. In Study AACG, a low number of subjects were enrolled with the following demographic characteristics: age less than 65 years, age 85 years or older, non-White race, and Hispanic ethnicity. Conclusions regarding the impact of these demographic characteristics on the frequency of adverse events cannot be drawn.

Adequacy of the safety database. The safety database does not fulfill minimum ICH guidance for exposure of at least 100 patients for 12 months at the proposed dose for drugs intended for long-term use. Therefore, the safety database is insufficient to adequately characterize the long-term safety of donanemab in the treatment of Alzheimer's disease.

Deaths. There were four deaths occurring in participants who received donanemab. No deaths were attributable to donanemab. There was not an excess of deaths in the donanemab arm of Study AACG compared to placebo. At the time of the 90-Day Safety Update, 22 deaths were reported from the main study of AACI, which is still blinded, with an additional death reported from that blinded study after the 90-Day Safety Update. Three of the blinded cases reported ARIA with fatal outcome.

SAEs. SAEs were reported with equal frequency in donanemab and placebo arms in Study AACG. Pneumonia was the most frequent SAE reported in Study AACG in the donanemab arm. Pneumonia was reported in 4% of participants in the donanemab arm compared to 1% on placebo. ARIA-E, infusion related reaction, pulmonary embolism, and syncope were reported in

2% of participants in the donanemab arm compared to none on placebo. In the all-donanemab pool, infection was the most frequently occurring SAE in the donanemab arm, occurring in 2% of participants.

AEs Leading to Drug or Study Discontinuations. Adverse events leading to study withdrawal were reported in 15% of donanemab-treated participants in Study AACG. The most frequent adverse events leading to study withdrawal in Study AACG were related to allergic reaction/hypersensitivity and ARIA-H microhemorrhage. Adverse events leading to treatment discontinuation were driven by protocol for ARIA events and infusion reactions. Adverse events leading to treatment discontinuation occurred in approximately 31% of donanemab-treated subjects in Study AACG. The most frequent adverse events leading to treatment discontinuation in Study AACG were adverse events related to allergic reaction/hypersensitivity, ARIA-E, ARIA-H superficial siderosis, and ARIA-H microhemorrhages.

Significant AEs. Evaluation of severe AEs did not identify a new safety signal.

Most Common AEs. The most common TEAEs in Study AACG were ARIA-E, ARIA-H Microhemorrhage, and ARIA-H Superficial Siderosis. In Study AACG, treatment emergent AEs with at least 5% risk (rounded) and at least 2% greater than placebo in the donanemab arm were: ARIA-E (27% and 1% on donanemab and placebo, respectively), ARIA-H Microhemorrhage (20% and 5% on donanemab and placebo, respectively), ARIA-H Superficial Siderosis (17% and 2% on donanemab and placebo, respectively), nausea/vomiting (13% and 5% on donanemab and placebo, respectively), infusion related reaction (8% and none on donanemab and placebo, respectively), urinary tract infection (10% and 4% on donanemab and placebo, respectively), diarrhea (8% and 4% on donanemab and placebo, respectively), and anxiety (5% and 2% on donanemab and placebo, respectively). TEAEs occurring in less than 5% of donanemab-treated participants and at least 2% more than placebo in Study AACG included bronchitis/lower respiratory tract infection, hypotension, and bradycardia.

Vital sign, laboratory, and ECG evaluations in Study AACG showed higher frequencies of bradycardia and orthostatic changes in diastolic blood pressure and TEAEs related to bradycardia and hypotension in donanemab-treated participants compared to placebo.

Pre-specified AE of interest:

Hepatic Safety – There was no signal of hepatotoxicity identified.

Immunogenicity - In the all-donanemab pool, 84% participants who were evaluable for treatment emergent anti-drug antibody (ADA) responses had a positive postbaseline treatment emergent ADA status. All of these participants also had neutralizing antibody present.

ARIA – ARIA has been observed in other amyloid-directed monoclonal antibody therapies for the treatment of AD. In blinded study AACI, three cases of ARIA had fatal outcome. No ARIA cases were reported to have fatal outcome in Study AACG or the all-donanemab pool. Serious ARIA-E cases were reported in 1% of participants in the all-donanemab-treated pool.

Symptomatic ARIA-E was reported in 3% of participants in the all-donanemab pool.

Intracerebral hemorrhage > 1 cm were reported in three subjects (0.2%) in the all-donanemab pool.

Hypersensitivity and infusion-related reactions – Serious cases of hypersensitivity and infusion

related reactions, including anaphylaxis, were observed in donanemab-treated participants. Serious infusion related reactions were reported in 2% of donanemab-treated participants compared to none on placebo in Study AACG. Increases and decreases in blood pressure and increases in heart rate were observed in participants with infusion related reactions. Suicidality - There was no evidence of an increased risk of suicidality with donanemab.

9. Advisory Committee Meeting and Other External Consultations

There was no FDA AC meeting.

10. Labeling Recommendations

10.1. Prescription Drug Labeling

The applicant submitted proposed labeling on May 18, 2022, at the time of the third and final submission of a rolling submission.

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

This reviewer recommends that in a future submission the prescribing information should include the observation of fatal cases of ARIA. This reviewer recommends the addition of class labeling language regarding the symptoms seen in some cases of ARIA and dose interruption recommendations.

This reviewer recommends that labeling include a Warnings and Precautions statements for ARIA and hypersensitivity and infusion related reactions. This reviewer recommends that increases and decreases in blood pressure and increases in heart rate observed in participants with infusion reactions be described in the Warnings and Precautions statement for hypersensitivity and infusion related reactions.

This reviewer recommends that the frequency of donanemab-treated participants with treatment emergent ADA responses and neutralizing antibodies be included in the immunogenicity section of labeling.

This reviewer recommends that the adverse reactions of hypotension and bradycardia be

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included under the Adverse Reactions table in Section 6 of labeling as less common adverse reactions observed with donanemab treatment.

10.2. Nonprescription Drug Labeling

Not applicable.

11. Risk Evaluation and Mitigation Strategies (REMS)

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

12. Postmarketing Requirements and Commitments

Not applicable.

13. Appendices

13.1. Summary of Cases with Fatal Outcome in the Blinded Main Study of AACI

Nineteen AEs with fatal outcome were reported in the safety population of the blinded main study of AACI.

Two of the AEs with fatal outcome were ARIA events and are summarize in the Deaths section of this review (ARIA-E, [I5T-MC-AACI-\(b\) \(6\)](#) and ARIA-H, [I5T-MC-AACI-\(b\) \(6\)](#)).

The following table contains this reviewer's summary of information in the remaining 17 events with fatal outcome from the blinded main study of AACI. The reviewer notes that 13 of the 17 cases had additional factors that were potential confounding factors, such as presence of medical history, concomitant medications, or concurrent events that were likely contributory to AEs with fatal outcome. Three of the 17 cases had onsets greater than 5-times the half-life of donanemab (preferred terms related to pneumonia (n=2) and pulmonary embolism). In the remaining case, the reviewer did not identify any known risk factor for the event of Suicide Attempt.

Table 75. Summary of 15 Cases of AEs with Fatal Outcome from Blinded Study AACI

USUBJID	Age/ Sex	AE onset Study Day	Notes
No identifiable risk factor			
I5T-MC-AACI- (b) (6) PT: Suicide Attempt	63 M	174	PMH of AD, circadian sleep disorder, hypothyroidism, and obstructive sleep apnea. In the two weeks preceding the event, he was noted to be more paranoid, anxious, confused, and had worsening vision and delusional behavior.
Cases lacked information on cause of death			
I5T-MC-AACI- (b) (6) 1 PT: Death	83 F	63	Patient died in her sleep. PMH of HTN, HL. Concomitant meds include alprazolam. The most recent dose of study drug was 35 days before. Information lacking in the case: no death certificate or results of an autopsy.
I5T-MC-AACI- (b) (6) PT: Death	85 M	19	Information lacking in the case: no death certificate or results of an autopsy.
PMH or concomitant medications were likely contributory to SAEs with fatal outcome			
I5T-MC-AACI- (b) (6) PT: Covid-19	79 M	346	PMH included AF, HTN, cardiomegaly, COPD. The patient presented to the ER unresponsive and was found to have a UTI and Covid pneumonia. He had received two doses of Covid vaccine. The most recent dose of study drug was 19 days prior to the event.
I5T-MC-AACI- (b) (6) PT: Subarachnoid hemorrhage	83 M	237	PMH unsteadiness and falls, CAD, and DM2. On acetylsalicylic acid (dose unknown). SAH occurred after fall from a ladder.
I5T-MC-AACI- (b) (6) PT: Myocardial Infarction	74 F	249	PMH of CAD, coronary angioplasty, TIA, HTN, HL
I5T-MC-AACI- (b) (6) PT: Retroperitoneal hemorrhage	82 F	267	On warfarin for PMH of AF. Also with concurrent events including thrombocytopenia and renal failure
I5T-MC-AACI- (b) (6)	69 F	3	PMH of mitral valve prolapse, atrial

USUBJID	Age/ Sex	AE onset Study Day	Notes
PT: Pulmonary embolism			fibrillation, sleep apnea, hereditary spherocytosis, and suspected sarcoidosis
I5T-MC-AACI- (b) (6) PT: Covid-19 pneumonia	82 M	70	PMH of chronic bronchitis, asthma, and COPD, DM2, unvaccinated for Covid-19
I5T-MC-AACI- (b) (6) PT: Dehydration	68 M	78	Death certificate notes cause of death as dehydration due to dysphagia and dementia.
I5T-MC-AACI- (b) (6) PT: Respiratory failure	85 M	17	PMH of DM2, obesity, OSA, who developed Covid-19 pneumonia on Study Day 3
Concurrent events likely contributory to SAEs with fatal outcome			
I5T-MC-AACI- (b) (6) PT: Alzheimer's dementia	84 F	154	Events preceding the AE include hospitalizations for Grade IV esophagitis, hypertensive emergency, NSTEMI
I5T-MC-AACI- (b) (6) PT: Respiratory fume inhalation disorder	83 F	176	Concurrent event includes house fire secondary to natural disaster
I5T-MC-AACI- (b) (6) PT: Pneumonia	81 M	126	Patient was hospitalized for new onset AF prior to developing pneumonia. PMH of HTN, HL, and tachycardia.
SAE onset > 57 days from most recent dose			
I5T-MC-AACI- (b) (6) PT: Pulmonary embolism	79 F	215	AE onset 74 days after most recent dose
I5T-MC-AACI- (b) (6) PT: Community acquired pneumonia	86 F	147	AE onset 147 days after most recent dose
I5T-MC-AACI- (b) (6) PT: Pneumonia and Sepsis	83 M	291	AE onset 58 days after the most recent dose

The reviewer created this table by reviewing narratives and CIOMS forms provided by the sponsor. AE: adverse event, AF: atrial fibrillation, CAD: coronary artery disease, COPD: chronic obstructive pulmonary disease, DM2: diabetes mellitus type 2, ER: emergency department, HL: hyperlipidemia, HTN: hypertension, NSTEMI: non-ST-elevation myocardial infarction, PMH: past medical history, PT: preferred term, OSA: obstructive sleep apnea, SAH: subarachnoid hemorrhage, TIA: transient ischemic attack, UTI: urinary tract infection.

90-Day Safety Update

At the time of the 90-Day Safety Update, an additional three AEs with fatal outcome were reported in the blinded main Study of AACI (preferred terms: completed suicide (n=2) respiratory arrest). A role for donanemab in the three AEs with fatal outcome could not be

established as treatment was still blinded. In the two cases with AEs of completed suicide, the participants had past medical history of depression as a risk factor (I5T-MC-AACI- (b) (6) and I5T-MC-AACI- (b) (6)). The reader is referred to the Deaths section of this review for further details on the cases. In the case of respiratory arrest with fatal outcome, concurrent events of gastric outlet obstruction, pancreatitis, and ureteropelvic junction obstruction were likely contributory factors (I5T-MC-AACI- (b) (6)).

13.2. Additional Narratives of Serious Cases of ARIA-E and ARIA-H

ARIA-E, ARIA-H (I5T-MC-AACG- (b) (6))

78-year-old female with past medical history of mild cognitive impairment, dyslipidemia, depression, hypothyroidism, APOE genotype carrier $\epsilon 4\epsilon 4$ who developed the SAEs of ARIA-E and ARIA-H, 63 days after starting treatment with donanemab, and 5 days since the third dose of donanemab. Concomitant medications included escitalopram. The patient's screening MRI showed cortical superficial siderosis in the left frontal lobe. She received her first infusion of donanemab on Study Day 55. On Study Day 117, she experienced difficulty reading all except discrete words. On Study Day 120, she experienced word output difficulty. On Study Day 127, she was unable to recognize her home. On Study Day 128, the patient's MRI scan showed a new occurrence of moderate plus ARIA-E in right and left frontal, temporal-non-hippocampal, parietal, and occipital lobes with extent of 5 to 10 centimeters. The MRI scan also showed ARIA-H with 18 microhemorrhages in right and left frontal, parietal, and occipital (all 3 each), and 4 mm superficial siderosis in the left frontal lobe. These findings were reported as the SAEs of moderate ARIA-E and ARIA-H. On Study Day 113, the study drug was temporarily interrupted for the SAEs of ARIA-E and ARIA-H. On Study Day 130, she developed alexia without agraphia and Gerstmann syndrome. On Study Day 133, the patient's condition worsened. She had difficulty understanding instructions and was hospitalized for ARIA-E and ARIA-H on that day. She was treated with pulse steroid and intravenous methyl prednisolone from Study Day 134 through 136. On Study Day 136, she was able to write full sentences and was discharged from the hospital on a prednisone taper for 20 days. On Study Day 157, she had persistent symptoms of difficulty with word expression, comprehension, reading, writing and confusion. She was given an additional 14 days of prednisone. On Study Day 168, an MRI showed ARIA-E in right and left occipital region with mild FLAIR hyperintensity confined to sulcus and/or cortex/sub cortex white matter, affecting an area of less than 5 cm. Compared to the previous MRI, the ARIA-E had decreased in size and there was no change in the number of microhemorrhages. There was 10 mm superficial siderosis in the left frontal region. On Study Day 190, the patient's symptoms worsened (unspecified) and an MRI on Study Day 192 showed complete resolution of ARIA-E. The MRI also showed 29 microhemorrhages at right and left frontal (6 each), right and left parietal (3 each), right and left occipital (5 each), and left cerebellum (1); and unchanged superficial siderosis. The ARIA-E was reported as resolved that day. On Study Day 201, she had worsening confusion associated with alexia, agraphia, and acalculia. On Study Day 217, the patient was unstable on her feet. The SAE of ARIA-H and symptoms of dyslexia,

aphasia, visual agnosia, intellectual disability associated with ARIA-E were reported as not resolved at the time of the data cut-off on Study Day 234.

Reviewer comment: A role for donanemab in the events of ARIA-E and ARIA-H is likely given the time between AE onset and dosing of donanemab, and because ARIA has been associated with aducanumab and lecanemab, approved amyloid-directed monoclonal antibody drugs.

ARIA-E, pneumonia, (15T-MC-AACG- (b) (6))

78-year-old female with history of AD, anaphylactic reaction and drug hypersensitivity (allergies to sulfa, methotrexate, and vicodin), APOE genotype carrier $\epsilon 4\epsilon 4$, who was found to have ARIA-E of severe severity on MRI scan performed on Study Day 73, 16 days after the 3rd dose of donanemab. In addition, the MRI showed 6 new areas of cortical superficial siderosis of the CNS. On Study Day 75, a CT scan of the head showed white matter disease and cerebral edema. On Study Day 75, 18 days after the 3rd dose of donanemab, the patient experienced an adverse event of moderate hypersensitivity/infusion related reaction characterized by vomiting and the SAE of right lower lobe pneumonia (severe in intensity). She presented to the ER with increased confusion, weakness, and emesis. She received ondansetron, azithromycin, ceftriaxone, and levofloxacin. Also on that day, she had moderate hypoglycemia, moderate asthenia, and moderate decreased appetite. The hypoglycemia resolved on Study Day 76 and the vomiting resolved on Study Day 77.

On Study Day 87, the patient was noted to back to her baseline mental status. The AE of decreased appetite and the SAE of pneumonia resolved on Study Day 115. On Study Day 173, ARIA-E was noted as recovered/resolved. The AEs of superficial siderosis of the CNS and asthenia was not recovered/resolved at the time of study completion. The study drug was permanently discontinued due to the SAE of ARIA-E per protocol.

Reviewer comment: A role for donanemab in the event of ARIA-E is likely given the time between AE onset and dosing of donanemab, and because ARIA has been associated with aducanumab and lecanemab, approved amyloid-directed monoclonal antibody drugs. A role for donanemab in the event of pneumonia cannot be ruled out given that the AE occurred within a time period when the patient was exposed to donanemab. Potentially contributory factors include the concurrent event of vomiting. Vomiting was identified as an infusion related reaction in the narrative; however, this appears unlikely given onset 15 days after the most recent infusion. Vomiting may be secondary to the SAE of ARIA-E as onset occurred within two days of onset of ARIA-E. The AE of superficial siderosis of the CNS is likely related to donanemab given that superficial siderosis of the CNS has been associated with aducanumab and lecanemab, approved amyloid-directed monoclonal antibody drugs.

13.3. TEAEs in Study AACG and Open-Label Studies

The following table shows TEAEs in Study AACG by preferred with frequency of at least 2% higher in the donanemab arm compared to placebo.

Table 76. TEAEs by Preferred Term with Frequency of at least 2% and at least 2% higher in the Donanemab Arm Compared to Placebo in Study AACG

Adverse Event	DON N=131 n (%)	Placebo N=125 n (%)
Amyloid Related Imaging Abnormality-edema/Effusion	35 (27)	1 (1)
Superficial Siderosis of Central Nervous System	18 (14)	4 (3)
Nausea	14 (11)	4 (3)
Infusion Related Reaction	10 (8)	0
Urinary Tract Infection	13 (10)	5 (4)
Cerebral Microhemorrhage	10 (8)	3 (2)
Amyloid Related Imaging Abnormality-Microhemorrhages and Hemosiderin Deposits	11 (8)	4 (3)
Diarrhea	11 (8)	5 (4)
Anxiety	7 (5)	2 (2)
Vomiting	7 (5)	3 (2)
Cataract	4 (3)	0
Hot Flush	3 (2)	0

The reviewer created this using the IDB ADAE dataset submitted in a response by the sponsor on August 5, 2022, to an information request dated August 2, 2022. SAFFL = Yes, StudyID=AACG, PCIN57FL = Yes, TRTEMFL = Yes.

The following table shows TEAEs in Study AACG by ODE-1 grouped terms with frequency of at least 2% higher in the donanemab arm compared to placebo.

Table 77. TEAEs by ODE-1 Grouped Terms with Frequency of at Least 2% and at Least 2% Higher in the Donanemab Arm Compared to Placebo in Study AACG

Adverse Event	DON N=131 n (%)	Placebo N=125 n (%)
Nausea/Vomiting MQG	17 (13)	6 (5)
Nausea	14 (11)	4 (3)
Vomiting	7 (5)	3 (2)
Allergic Reaction and Hypersensitivity MQG	13 (10)	4 (3)
Infusion Related Reaction	10 (8)	0
Allergic Dermatitis	1 (1)	0

Adverse Event	DON N=131 n (%)	Placebo N=125 n (%)
Drug Eruption	1 (1)	0
Urticaria	1 (1)	0
Angioedema	0	1 (1)
Face edema	0	1 (1)
Hypersensitivity	0	1 (1)
Pharyngeal Swelling	0	1 (1)
Infusion Site Reaction, Infusion Reaction MQG	10 (8)	1 (1)
Infusion Related Reaction	10 (8)	0
Infusion Site Swelling	0	1 (1)
Intracranial Hemorrhage MQG	10 (8)	4 (3)
Cerebral Microhemorrhage	9 (7)	3 (2)
Extradural Hematoma	1 (1)	0
Subdural Hematoma	1 (1)	0
Intraventricular Hemorrhage	0	1 (1)
Bleeding MQG	16 (12)	10 (8)
Cerebral Microhemorrhage	9 (7)	3 (2)
Conjunctival Hemorrhage	2 (2)	0
Hemoptysis	2 (2)	0
Extradural Hematoma	1 (1)	0
Occult Blood Positive	1 (1)	0
Optic Disc Hemorrhage	1 (1)	0
Subdural Hematoma	1 (1)	0
Traumatic Hematoma	1 (1)	1 (1)
Ecchymosis	0	1 (1)
Hematochezia	0	1 (1)
Intraventricular Hemorrhage	0	1 (1)
Melena	0	1 (1)
Vessel Puncture Site Bruise	0	2 (2)
Bronchitis, Bronchiolitis, Tracheitis, Alveolitis, Bronchiectasis MQG	6 (5)	2 (2)
Bronchitis	4 (3)	2 (2)
Viral Bronchitis	1 (1)	0
Lower Respiratory Tract Infection	1 (1)	0
Infection MQG	45 (34)	40 (32)
Urinary Tract Infection	13 (10)	5 (4)
Skin Infection	2 (2)	0

Adverse Event	DON N=131 n (%)	Placebo N=125 n (%)
Bacterial Sepsis	1 (1)	0
Bronchitis	4 (3)	2 (2)
Viral Bronchitis	1 (1)	0
Fungal Infection	1 (1)	0
Hordeolum	1 (1)	0
Influenza	2 (2)	1 (1)
Lower Respiratory Tract Infection	1 (1)	0
Oral Herpes	1 (1)	0
Pneumonia	7 (5)	5 (4)
Cellulitis	2 (2)	2 (2)
Clostridium Difficile Colitis	1 (1)	1 (1)
Laryngitis	1 (1)	1 (1)
Nasopharyngitis	6 (5)	6 (5)
Tooth Abscess	1 (1)	1 (1)
Upper Respiratory Tract Infection	9 (7)	9 (7)
Viral Upper Respiratory Tract Infection	1 (1)	1 (1)
Cholecystitis	0	1 (1)
Eyelid Infection	0	1 (1)
Fungal Skin Infection	0	1 (1)
Gastroenteritis	1 (1)	2 (2)
Gastrointestinal Viral Infection	0	1 (1)
Influenza Like Illness	0	1 (1)
Localized Infection	0	1 (1)
Lyme Disease	1 (1)	2 (2)
Onychomycosis	0	1 (1)
Aspiration Pneumonia	0	1 (1)
Sinusitis	1 (1)	2 (2)
Staphylococcal Infection	0	1 (1)
Testicular Abscess	0	1 (1)
Tooth Infection	0	1 (1)
Herpes Zoster	0	3 (2)
Diarrhea, Colitis, Enteritis, Proctitis,	12 (9)	9 (7)
Diarrhea	11 (8)	5 (4)
Ischemic Colitis	1 (1)	0
Clostridium Difficile Colitis	1 (1)	1 (1)
Gastroenteritis	1 (1)	2 (2)

Adverse Event	DON N=131 n (%)	Placebo N=125 n (%)
Gastrointestinal Viral Infection	0	1 (1)
Dermatitis MQG	5 (4)	3 (2)
Allergic Dermatitis	1 (1)	0
Bullous Dermatitis	1 (1)	0
Dermatitis	1 (1)	1 (1)
Contact Dermatitis	1 (1)	1 (1)
Seborrheic Dermatitis	1 (1)	1 (1)
Bradycardia MQG	3 (2)	0
Sinus Bradycardia	2 (2)	0
Bradycardia	1 (1)	0

MQG: MedDRA Query Group. The reviewer created this using the IDB ADAE dataset submitted in a response by the sponsor on August 5, 2022, to an information request dated August 2, 2022. SAFFL = Yes, StudyID=AACG, PCIN57FL = Yes, TRTEMFL = Yes.

The following table shows TEAEs in Study AACG by FDA Narrow grouped terms with frequency of at least 2% higher in the donanemab arm compared to placebo.

Table 78. TEAEs by FDA Narrow Grouped Terms with Frequency of at Least 2% and at Least 2% Higher in the Donanemab Arm Compared to Placebo in Study AACG

Adverse Event	DON N=131 n (%)	Placebo N=125 n (%)
Local Administration Reactions Fda N MQG	10 (8)	2 (2)
Infusion Related Reaction	10 (8)	0
Injection Site Pruritus	1 (1)	0
Infusion Site Swelling	0	1 (1)
Injection Site Pain	0	1 (1)
Arrhythmia Fda N MQG	10 (8)	6 (5)
Sinus Bradycardia	2 (2)	0
Bradycardia	1 (1)	0
Sinus Arrhythmia	1 (1)	0
Sinus Node Dysfunction	1 (1)	0
Tachycardia	1 (1)	0
Atrial Fibrillation	3 (2)	3 (2)
Ventricular Extrasystoles	1 (1)	1 (1)
Atrial Flutter	1 (1)	2 (2)
Anxiety Fda N MQG	7 (5)	3 (2)

Adverse Event	DON N=131 n (%)	Placebo N=125 n (%)
Anxiety	7 (5)	2 (2)
Procedural Anxiety	0	1 (1)
Hypotension Fda N MQG	6 (5)	3 (2)
Orthostatic Hypotension	2 (2)	0
Hypotension	4 (3)	3 (2)
Fatigue Fda N MQG	10 (8)	8 (6)
Asthenia	4 (3)	3 (2)
Lethargy	1 (1)	0
Fatigue	5 (4)	5 (4)
Malaise	0	1 (1)
Cough Fda N MQG	4 (3)	1 (1)
Hemoptysis	2 (2)	0
Upper-Airway Cough Syndrome	2 (2)	0
Cough	0	1 (1)

MQG: MedDRA Query Group. The reviewer created this using the IDB ADAE dataset submitted in a response by the sponsor on August 5, 2022, to an information request dated August 2, 2022. SAFFL = Yes, StudyID=AACG, PCIN57FL = Yes, TRTEMFL = yes.

The following table shows the most common TEAEs reported within the first twelve weeks of treatment. Symptomatic ARIA-E occurred in 4 subjects in the donanemab arm (3%) compared to none on placebo in Study Days 1 through 84 in Study AACG.

Table 79. TEAEs Occurring in Study Days 1 through 84 in Study AACG

AEs	Donanemab N=131 n (%)	Placebo N=125 n (%)
ARIA-E ¹	21 (16)	0
ARIA-H Superficial Siderosis ¹	12 (9)	1 (1)
ARIA-H Microhemorrhage ¹	10 (8)	2 (2)
Infusion Related Reaction	3 (2)	0
Cataract	2 (2)	0
Hypoglycemia	2 (2)	0
Hypotension	2 (2)	0
Skin Infection	2 (2)	0
Squamous Cell Carcinoma	2 (2)	0

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

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

The following table shows TEAEs by ODE-1 grouped terms with frequency of at least 5% in the all-donanemab pool at the time of the 90-Day Safety Update.

Table 80. TEAEs by ODE-1 Grouped Terms with Frequency of at Least 5% in the All-Donanemab Pool in the 90-Day Safety Update.

Adverse Event	DON N=1304 n (%)
Infection MQG	197 (15)
Urinary Tract Infection	48 (4)
Upper Respiratory Tract Infection	29 (2)
Nasopharyngitis	20 (2)
Pneumonia	18 (1)
Sinusitis	17 (1)
Bronchitis	9 (1)
Cellulitis	9 (1)
Diverticulitis	8 (1)
Ear Infection	4 (<0.5)
Gastroenteritis	4 (<0.5)
Influenza	4 (<0.5)
Tooth Abscess	4 (<0.5)
Tooth Infection	4 (<0.5)
Hordeolum	3 (<0.5)
Vulvovaginal Mycotic Infection	3 (<0.5)
Chronic Sinusitis	2 (<0.5)
Herpes Zoster	2 (<0.5)
Kidney Infection	2 (<0.5)
Onychomycosis	2 (<0.5)
Orchitis	2 (<0.5)
Skin Infection	2 (<0.5)
Subcutaneous Abscess	2 (<0.5)
Viral Rhinitis	2 (<0.5)
Acute Sinusitis	1 (<0.5)
Bacterial Arthritis	1 (<0.5)
Bacterial Sepsis	1 (<0.5)
Viral Bronchitis	1 (<0.5)
Campylobacter Infection	1 (<0.5)

Adverse Event	DON N=1304 n (%)
Cholecystitis	1 (<0.5)
Acute Cholecystitis	1 (<0.5)
Clostridium Difficile Colitis	1 (<0.5)
Cystitis	1 (<0.5)
Infected Dermatitis	1 (<0.5)
Eye Infection	1 (<0.5)
Folliculitis	1 (<0.5)
Fungal Infection	1 (<0.5)
Fungal Esophagitis	1 (<0.5)
Fungal Skin Infection	1 (<0.5)
Furuncle	1 (<0.5)
Influenza Like Illness	1 (<0.5)
Laryngitis	1 (<0.5)
Lower Respiratory Tract Infection	1 (<0.5)
Lyme Disease	1 (<0.5)
Oral Herpes	1 (<0.5)
Oral Infection	1 (<0.5)
Otitis Media	1 (<0.5)
Acute Otitis Media	1 (<0.5)
Peritoneal Abscess	1 (<0.5)
Peritonitis	1 (<0.5)
Aspiration Pneumonia	1 (<0.5)
Klebsiella Pneumonia	1 (<0.5)
Post Procedural Infection	1 (<0.5)
Respiratory Tract Infection	1 (<0.5)
Rhinitis	1 (<0.5)
Rhinovirus Infection	1 (<0.5)
Salmonellosis	1 (<0.5)
Sepsis	1 (<0.5)
Sinobronchitis	1 (<0.5)
Staphylococcal Infection	1 (<0.5)
Staphylococcal Skin Infection	1 (<0.5)
Testicular Abscess	1 (<0.5)
Bacterial Urinary Tract Infection	1 (<0.5)
Viral Upper Respiratory Tract Infection	1 (<0.5)
Wound Infection	1 (<0.5)

Adverse Event	DON N=1304 n (%)
Headache MQG	136 (10)
Headache	124 (10)
Migraine	6 (<0.5)
Tension Headache	3 (<0.5)
Procedural Headache	2 (<0.5)
Post-Traumatic Headache	1 (<0.5)
Allergic Reaction and Hypersensitivity MQG	132 (10)
Infusion Related Reaction	115 (9)
Hypersensitivity	5 (<0.5)
Urticaria	5 (<0.5)
Anaphylactic Reaction	4 (<0.5)
Allergic Dermatitis	2 (<0.5)
Allergic Conjunctivitis	1 (<0.5)
Drug Eruption	1 (<0.5)
Face Swelling	1 (<0.5)
Fall, Dizziness, Balance Disorder MQG	118 (9)
Fall	70 (5)
Dizziness	46 (4)
Balance Disorder	8 (1)
Gait Disturbance	6 (<0.5)
Postural Dizziness	2 (<0.5)
Upper Respiratory Infection, Cold, Rhinitis, Upper Respiratory Tract Infection MQG	71 (5)
Upper Respiratory Tract Infection	29 (2)
Nasopharyngitis	20 (2)
Sinusitis	17 (1)
Chronic Sinusitis	2 (<0.5)
Viral Rhinitis	2 (<0.5)
Acute Sinusitis	1 (<0.5)
Influenza Like Illness	1 (<0.5)
Laryngitis	1 (<0.5)
Respiratory Tract Infection	1 (<0.5)
Rhinitis	1 (<0.5)
Sinobronchitis	1 (<0.5)
Viral Upper Respiratory Tract Infection	1 (<0.5)

MQG: MedDRA Query Group. The reviewer created this using the 90-Day Safety IDB ADAE dataset submitted 8.25.22, TRT01A = inversion of Dona-C, SAFFL = Yes, LYIN57FL = Yes, TRTEMFL = Yes.

The following table shows TEAEs by FDA Narrow Grouped Terms with frequency of at least 5% in the all-donanemab pool at the time of the 90-Day Safety Update.

Table 81. TEAEs by FDA Narrow Grouped Terms with Frequency of at Least 5% in the All-Donanemab Pool in the 90-Day Safety Update.

Adverse Event	DON N=1304 n (%)
Headache Fda N MQG	138 (11)
Headache	124 (10)
Migraine	6 (<0.5)
Tension Headache	3 (<0.5)
Cervicogenic Headache	2 (<0.5)
Procedural Headache	2 (<0.5)
Drug Withdrawal Headache	1 (<0.5)
Occipital Neuralgia	1 (<0.5)
Post-Traumatic Headache	1 (<0.5)
Local Administration Reactions Fda N MQG	121 (9)
Infusion Related Reaction	115 (9)
Infusion Site Extravasation	4 (<0.5)
Infusion Site Reaction	1 (<0.5)
Injection Site Pruritus	1 (<0.5)
Vaccination Site Pain	1 (<0.5)
Hemorrhage Fda N MQG	74 (6)
Cerebral Microhemorrhage	23 (2)
Contusion	9 (1)
Conjunctival Hemorrhage	6 (<0.5)
Epistaxis	5 (<0.5)
Subdural Hematoma	5 (<0.5)
Bone Contusion	4 (<0.5)
Hematuria	4 (<0.5)
Cerebellar Microhemorrhage	2 (<0.5)
Cerebral Hematoma	2 (<0.5)
Hemoptysis	2 (<0.5)
Subarachnoid Hemorrhage	2 (<0.5)
Blood Loss Anemia	1 (<0.5)
Cerebral Hemorrhage	1 (<0.5)
Cystitis Hemorrhagic	1 (<0.5)

Adverse Event	DON N=1304 n (%)
Ecchymosis	1 (<0.5)
Extradural Hematoma	1 (<0.5)
Gastrointestinal Hemorrhage	1 (<0.5)
Hematochezia	1 (<0.5)
Hematoma	1 (<0.5)
Hemorrhage	1 (<0.5)
Hemorrhagic Stroke	1 (<0.5)
Hemothorax	1 (<0.5)
Melena	1 (<0.5)
Optic Disc Hemorrhage	1 (<0.5)
Periorbital Hematoma	1 (<0.5)
Subcutaneous Hematoma	1 (<0.5)
Traumatic Hematoma	1 (<0.5)
Vaginal Hemorrhage	1 (<0.5)
Dizziness Fda N MQG	66 (5)
Dizziness	45 (3)
Balance Disorder	8 (1)
Vertigo	7 (1)
Presyncope	4 (<0.5)
Postural Dizziness	2 (<0.5)
Meniere's Disease	1 (<0.5)
Positional Vertigo	1 (<0.5)

MQG: MedDRA Query Group. The reviewer created this using the 90-Day Safety IDB ADAE dataset submitted 8.25.22, TRT01A = inversion of Dona-C, SAFFL = Yes, LYIN57FL = Yes, TRTEMFL = Yes.

The following table shows TEAEs by preferred terms that contributed to the grouping of ARIA-H Microhemorrhage MQG in the All-Donanemab pool at the time of the 90-Day Safety Update.

Table 82. TEAEs by ARIA-H Microhemorrhage MQG in the All-Donanemab Pool in the 90-Day Safety Update.

Adverse Event	DON N=1304 n (%)
ARIA-H Microhemorrhage MQG	165 (13)
Amyloid Related Imaging Abnormality-Microhemorrhages and Hemosiderin Deposits	144 (11)
Cerebellar Microhemorrhage	2 (<0.5)

Cerebral Microhemorrhage	23 (2)

MQG: MedDRA Query Group. The reviewer created this using the 90-Day Safety IDB ADAE dataset submitted 8.25.22, TRT01A = inversion of Dona-C, SAFFL = Yes, LYIN57FL = Yes, TRTEMFL = Yes.

13.4. MedDRA Query Groups

The following is a list of MedDRA query groups referenced in this review and the preferred terms that contribute to the group. All preferred terms that contribute to their respective groups are listed even though the preferred term may have not been reported within the clinical program.

Allergic Reaction and Hypersensitivity MQG

Allergic bronchitis; allergic edema; allergic pharyngitis; allergic sinusitis; allergic transfusion reaction; allergy to vaccine; alveolitis allergic; anaphylactic reaction; anaphylactic shock; anaphylactic transfusion reaction; anaphylactoid reaction; angiedema; angioneurotic edema; auricular swelling; blepharitis allergic; bronchopulmonary aspergillosis allergic; circumoral edema; conjunctivitis allergic; contrast media allergy; dermatitis allergic; dermatitis atopic; device allergy; drug eruption; drug hypersensitivity; drug rash with eosinophilia and systemic symptoms; ear swelling; epiglottic edema; face edema; fixed eruption; fuchs' syndrome; hypersensitivity; infusion related reaction; injection related reaction; injection site atrophy; injection site discomfort; injection site hypersensitivity; injection site hypertrophy; injection site irritation; injection site macule; injection site necrosis; injection site plaque; injection site scab; injection site scar; injection site vesicles; laryngeal edema; laryngitis allergic; laryngospasm; lip edema; lip swelling; multiple allergies; nephritis allergic; oropharyngeal spasm; palatal edema; pharyngeal edema; pharyngeal swelling; photosensitivity allergic reaction; swelling face; swollen tongue; tongue edema; urticaria; urticaria cholinergic; urticaria chronic; urticaria generalised; urticaria localised; urticaria pigmentosa; and vasculitic rash.

Anxiety Fda N MQG

Acrophobia; adjustment disorder with anxiety; adjustment disorder with mixed anxiety and depressed mood; aerophobia; agoraphobia; aids phobia; alcohol withdrawal syndrome; algophobia; animal phobia; anticipatory anxiety; anxiety; anxiety aggravated; anxiety disorder; anxiety disorder due to a general medical condition; anxiety disorder nec; anxiety nec; anxiety postoperative; arachnophobia; astraphobia; autophobia; cancerphobia; cardiac neurosis; cibophobia; claustrophobia; compulsive cheek biting; compulsive handwashing; compulsive lip biting; dysmorphophobia; emetophobia; exacerbation of anxiety; exaggerated startle response; fear; fear of animals; fear of closed spaces; fear of crowded places; fear of death; fear of disease; fear of eating; fear of falling; fear of injection; fear of needles; fear of open spaces; fear of pregnancy; fear of weight gain; fear-related avoidance of activities; generalised anxiety disorder; glossophobia; hemophobia; haphephobia; herpetophobia; hydrophobia; hypervigilance; illness anxiety disorder; immunisation anxiety related reaction; kinesiophobia; limited symptom panic attack; mixed anxiety and depressive disorder; monophobia;

mysophobia; nail picking; nervousness; neurosis; neurosis nos; noctiphobia; nocturnal fear; nosophobia; obsessive need for symmetry; obsessive-compulsive disorder; obsessive-compulsive symptom; ochlophobia; osmophobia; panic attack; panic disorder; panic disorder nos; panic disorder with agoraphobia; panic disorder without agoraphobia; panic reaction; panic reaction aggravated; paruresis; pathological doubt; performance fear; phagophobia; pharmacophobia; phobia; phobia of driving; phobia of exams; phobia of flying; phobias nos; phobic avoidance; phobic disorder aggravated; phobic postural vertigo; phonophobia; photaugiaphobia; postpartum anxiety; postpartum neurosis; procedural anxiety; pseudoangina; selective mutism; separation anxiety disorder; sitophobia; social anxiety disorder; social fear; social phobia; stress; stress symptoms; tension; thanatophobia; thermophobia; trichotemnomania; trichotillomania; and white coat hypertension.

Arrhythmia FDA N MQG

Accelerated idioventricular rhythm; agonal rhythm; arrhythmia; arrhythmia neonatal; arrhythmia nos; arrhythmia nos fetal; arrhythmia nos neonatal; arrhythmia supraventricular; atrial bigeminy; atrial fibrillation; atrial fibrillation aggravated; atrial flutter; atrial flutter with 1:1 atrioventricular conduction; atrial parasystole; atrial tachycardia; atrioventricular extrasystoles; bradyarrhythmia; bradycardia; bradycardia fetal; bradycardia neonatal; bradycardia nos; bradytachycardia; cardiac fibrillation; cardiac fibrillation nos; cardiac flutter; central bradycardia; congenital supraventricular tachycardia; extrasystoles; extrasystoles nos; fetal arrhythmia; fetal tachyarrhythmia; junctional ectopic tachycardia; neonatal bradyarrhythmia; neonatal sinus bradycardia; neonatal sinus tachycardia; neonatal tachyarrhythmia; neonatal tachycardia; nodal arrhythmia; pacemaker generated arrhythmia; parasystole; parasystolia; paroxysmal arrhythmia; pulsus bigeminus; rebound tachycardia; reperfusion arrhythmia; reperfusion arrhythmias; rhythm idioventricular; sick sinus syndrome; sinoatrial node dysfunction; sinus arrhythmia; sinus bradycardia; sinus node dysfunction; sinus tachycardia; supraventricular arrhythmia nos; supraventricular extrasystoles; supraventricular tachyarrhythmia; supraventricular tachycardia; tachyarrhythmia; tachycardia; tachycardia aggravated; tachycardia fetal; tachycardia irregular; tachycardia nos; tachycardia paroxysmal; tachycardia paroxysmal nos; tachycardia supraventricular aggr; torsade de pointes; trigeminy; ventricular arrhythmia; ventricular arrhythmia nos; ventricular bigeminy; ventricular extrasystoles; ventricular fibrillation; ventricular fibrillation and flutter; ventricular flutter; ventricular parasystole; ventricular quadrigeminy; ventricular tachyarrhythmia; ventricular tachycardia; ventricular trigeminy; wandering pacemaker; and withdrawal arrhythmia.

Asthenia, Fatigue, Malaise, Weakness, Narcolepsy MQG

Asthenia; chronic fatigue syndrome; exercise capacity decreased; fatigue; hemiplegia; listless; malaise; mental fatigue; muscular weakness; myasthenic syndrome; narcolepsy; sedation; sleep attacks; and sluggishness

Clinical Review
Natalie Branagan, MD
BLA 761248
Kisunla/donanemab

Ataxia, Cerebellar Syndrome MQG

Ataxia; cerebellar ataxia; cerebellar ischemia; cerebellar syndrome; coordination abnormal; friedreich's ataxia; and vestibular ataxia.

Bleeding MQG

Abdominal hematoma; abdominal wall hematoma; abdominal wall hemorrhage; abnormal withdrawal bleeding; administration site hemorrhage; adrenal hemorrhage; anal hemorrhage; anal ulcer hemorrhage; anastomotic hemorrhage; anastomotic ulcer hemorrhage; antepartum hemorrhage; aortic intramural hematoma; application site bleeding; application site bruise; application site hematoma; arterial hemorrhage; auricular hematoma; basal ganglia hemorrhage; bleeding varicose vein; blood urine; blood urine present; bloody discharge; brain contusion; brain stem hemorrhage; breast hematoma; breast hemorrhage; bronchial hemorrhage; catheter site hematoma; catheter site hemorrhage; cephalhematoma; cerebellar hematoma; cerebral hematoma; cerebral hemorrhage; cerebral hemorrhage traumatic; cerebral microhemorrhage; cervix hematoma uterine; cervix hemorrhage uterine; choroidal hemorrhage; chronic gastrointestinal bleeding; coital bleeding; colonic hematoma; colonic hemorrhage; conjunctival hemorrhage; corneal bleeding; cystitis hemorrhagic; diarrheahemorrhagic; diverticulitis intestinal hemorrhagic; diverticulum intestinal hemorrhagic; duodenal ulcer hemorrhage; duodenitis hemorrhagic; dysentery; dysfunctional uterine bleeding; ear hemorrhage; ecchymosis; enterocolitis hemorrhagic; epistaxis; extradural hematoma; extravasation blood; eye hemorrhage; eyelid bleeding; eyelid hematoma; gastric hemorrhage; gastric occult blood positive; gastric ulcer hemorrhage; gastric varices hemorrhage; gastritis hemorrhagic; gastroduodenitis hemorrhagic; gastrointestinal hemorrhage; gastrointestinal polyp hemorrhage; genital hemorrhage; gingival bleeding; hemarthrosis; hematemesis; hematochezia; hematoma; hematospermia; hematotympanum; hematuria traumatic; hemobilia; hemoglobin urine present; hemopneumothorax; hemoptysis; hemorrhage; hemorrhage coronary artery; hemorrhage intracranial; hemorrhage subcutaneous; hemorrhage subepidermal; hemorrhage urinary tract; hemorrhagic arteriovenous malformation; hemorrhagic ascites; hemorrhagic cerebral infarction; hemorrhagic cyst; hemorrhagic erosive gastritis; hemorrhagic ovarian cyst; hemorrhagic stroke; hemorrhagic thyroid cyst; hemorrhagic transformation stroke; hemorrhoidal hemorrhage; hemothorax; hepatic hematoma; hyphema; implant site hematoma; implant site hemorrhage; incision site hematoma; incision site hemorrhage; infusion site hematoma; infusion site hemorrhage; injection site hemorrhage; intestinal hematoma; intestinal hemorrhage; intestinal polyp hemorrhage; intra-abdominal hematoma; intra-abdominal hemorrhage; intracranial hematoma; intraocular hematoma; intraventricular hemorrhage; lacrimal hemorrhage; large intestinal hemorrhage; large intestinal ulcer hemorrhage; laryngeal hemorrhage; lip hemorrhage; melaena; mouth hemorrhage; mucosal hemorrhage; muscle hemorrhage; myocardial hemorrhage; naevus hemorrhage; nail bed bleeding; occult blood; occult blood positive; esophageal hemorrhage; esophageal ulcer hemorrhage; esophageal varices hemorrhage; esophagitis hemorrhagic; operative hemorrhage; optic disc hemorrhage; ovarian

hemorrhage; paranasal sinus hematoma; pelvic hematoma; penile hematoma; penile hemorrhage; peptic ulcer hemorrhage; pericardial hemorrhage; periorbital hematoma; periorbital hemorrhage; perirenal hematoma; peritoneal hemorrhage; pharyngeal hematoma; pharyngeal hemorrhage; pleural hemorrhage; post procedural hematoma; post procedural hematuria; post procedural hemorrhage; postmenopausal hemorrhage; postpartum hemorrhage; procedural hemorrhage; proctitis hemorrhagic; prostatic hemorrhage; pulmonary alveolar hemorrhage; pulmonary hemorrhage; puncture site hemorrhage; putamen hemorrhage; rectal hemorrhage; rectal ulcer hemorrhage; renal cyst hemorrhage; renal hematoma; renal hemorrhage; respiratory tract hemorrhage; retinal hemorrhage; retinopathy hemorrhagic; retroperitoneal hematoma; retroperitoneal hemorrhage; ruptured cerebral aneurysm; scleral hemorrhage; scrotal hematocele; scrotal hematoma; shock hemorrhagic; skin bleeding; skin hemorrhage; skin neoplasm bleeding; skin ulcer hemorrhage; small intestinal hemorrhage; soft tissue hemorrhage; spinal cord hemorrhage; spinal hematoma; splenic hemorrhage; spontaneous hematoma; spontaneous hemorrhage; stoma site hemorrhage; subarachnoid hemorrhage; subchorionic hematoma; subcutaneous hematoma; subdural hematoma; subdural hemorrhage; subgaleal hematoma; testicular hemorrhage; thalamus hemorrhage; thoracic hemorrhage; thrombocytopenic purpura; tongue hematoma; tongue hemorrhage; tooth socket hemorrhage; traumatic hematoma; traumatic hemorrhage; traumatic hemothorax; traumatic intracranial hemorrhage; tumorhemorrhage; ulcer hemorrhage; umbilical hemorrhage; upper gastrointestinal hemorrhage; urethral hemorrhage; urinary bladder hemorrhage; urogenital hemorrhage; uterine hemorrhage; vaccination site hematoma; vaginal hematoma; vaginal hemorrhage; venous hemorrhage; vessel puncture site bruise; vessel puncture site hematoma; vessel puncture site hemorrhage; vitreous hemorrhage; vulval hemorrhage; wound hematoma; and wound hemorrhage.

Bradycardia MQG

Bradyarrhythmia; bradycardia; bradycardia fetal; bradycardia neonatal; fetal heart rate; deceleration abnormality; heart rate decreased; and sinus bradycardia.

Bronchitis, Bronchiolitis, Tracheitis, Alveolitis, Bronchiectasis MQG

Allergic bronchitis; alveolitis; bacterial tracheitis; bronchial infection; bronchiectasis; bronchiolitis; bronchitis; bronchitis acute; bronchitis acute viral; bronchitis bacterial; bronchitis chemical; bronchitis chronic; bronchitis fungal; bronchitis pneumococcal; bronchitis viral; bronchopneumopathy; bronchopulmonary aspergillosis allergic; fungal tracheitis; infective exacerbation of bronchiectasis; lower respiratory tract infection; lower respiratory tract infection bacterial; lower respiratory tract infection fungal; lower respiratory tract infection viral; lung infection; lung infection pseudomonal; obstructive chronic bronchitis with acute exacerbation; pseudomonas bronchitis; pulmonary mycosis; rhinotracheitis; sinobronchitis; tracheitis; tracheobronchitis; and tracheobronchitis viral

Confusion, Delirium, Altered Mental Status, Disorientation, Coma MQG

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Altered state of consciousness; apallic syndrome; catatonia; cerebral circulatory failure; coma; coma hepatic; confusion postoperative; confusional state; decerebration; delirium; depressed level of consciousness; diabetic hyperosmolar coma; disorientation; dissociative fugue; disturbance in attention; hypercapnic coma; hypoglycemic coma; hypoglycemic unconsciousness; hypoxic-ischemic encephalopathy; incoherent; lethargy; mental impairment; mental status changes; shock hypoglycemic; somnolence; stupor; transient global amnesia; traumatic coma; unresponsive to stimuli; and vascular dementia

Cough Fda N MQG

Allergic cough; cough; primary cough headache; productive cough; and upper-airway cough syndrome

Dermatitis MQG

Acarodermatitis; administration site dermatitis; angiodermatitis; application site dermatitis; catheter site dermatitis; dermatitis; dermatitis acneiform; dermatitis allergic; dermatitis atopic; dermatitis bullous; dermatitis contact; dermatitis diaper; dermatitis exfoliative; dermatitis infected; dermatitis psoriasiform; hand dermatitis; herpes dermatitis; implant site dermatitis; neurodermatitis; perivascular dermatitis; photodermatitis; seborrheic dermatitis; solar dermatitis; and stasis dermatitis

Diarrhea, Colitis, Enteritis, Proctitis MQG

Acute hemorrhagic ulcerative colitis; amoebic dysentery; campylobacter gastroenteritis; campylobacter infection; campylobacter intestinal infection; clostridial infection; clostridium colitis; clostridium difficile colitis; clostridium test positive; colitis; colitis erosive; colitis ischemic; colitis microscopic; colitis psychogenic; colitis ulcerative; colon dysplasia; colonic obstruction; crohn's disease; cytomegalovirus colitis; diarrhea; diarrhea hemorrhagic; diarrhea infectious; dysentery; enteritis; enteritis infectious; enteritis; ecroticans; enterocele; enterocolitis; enterocolitis bacterial; enterocolitis fungal; enterocolitis hemorrhagic; enterocolitis infectious; enterocolitis viral; gastroenteritis; gastroenteritis adenovirus; gastroenteritis aeromonas; gastroenteritis bacterial; gastroenteritis clostridial; gastroenteritis cryptosporidial; gastroenteritis enteroviral; gastroenteritis escherichia coli; gastroenteritis norovirus; gastroenteritis norwalk virus; gastroenteritis rotavirus; gastroenteritis salmonella; gastroenteritis viral; gastrointestinal candidiasis; gastrointestinal infection; gastrointestinal inflammation; gastrointestinal viral infection; inflammatory bowel disease; intestinal ischemia; intestinal perforation; large intestinal ulcer; large intestine perforation; mechanical ileus; necrotising colitis; parasitic infection intestinal; post procedural diarrhea; pseudomembranous colitis; and sigmoiditis viral diarrhea

Dizziness Fda N MQG

Acute vestibular syndrome; balance disorder; cervicogenic vertigo; dizziness; dizziness (excl vertigo); dizziness aggravated; dizziness exertional; dizziness postural; epidemic vertigo;

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labyrinthitis; meniere's disease; meniere's disease aggravated; persistent postural-perceptual dizziness; post procedural dizziness; postoperative dizziness; presyncope; procedural dizziness; vasovagal attack; vertigo; vertigo aggravated; vertigo cns origin; vertigo labyrinthine; vertigo nec; vertigo positional; vestibular neuronitis; and viral labyrinthitis

Fall, Dizziness, Balance Disorder MQG

Balance disorder; dizziness; dizziness exertional; dizziness postural; fall; gait disturbance; procedural dizziness; and progressive supranuclear palsy

Fatigue Fda N MQG

Asthenia; cancer fatigue; chronic fatigue syndrome; debility; fatigue; fatigue aggravated; lethargy; listless; malaise; mental fatigue; neurasthenia; post viral fatigue syndrome; prostration; sluggishness; and weakness

Fracture MQG

Acetabulum fracture; ankle fracture; avulsion fracture; cervical vertebral fracture; clavicle fracture; comminuted fracture; compression fracture; epiphyseal fracture; external fixation of fracture; facial bones fracture; femoral neck fracture; femur fracture; fibula fracture; foot fracture; forearm fracture; fracture; fracture displacement; fracture malunion; fractured coccyx; fractured ischium; fractured sacrum; hand fracture; hip fracture; humerus fracture; internal fixation of fracture; jaw fracture; lower limb fracture; lumbar vertebral fracture; multiple fractures; open fracture; osteoporotic fracture; patella fracture; pathological fracture; pelvic fracture; periprosthetic fracture; pubis fracture; radius fracture; rib fracture; scapula fracture; skull fracture; skull fractured base; spinal compression fracture; spinal fracture; sternal fracture; stress fracture; thoracic vertebral fracture; tibia fracture; traumatic fracture; ulna fracture; upper limb fracture; and wrist fracture

Headache Fda N MQG

Basilar migraine; cervicogenic headache; chronic paroxysmal hemicrania; cluster headache; cluster headaches; cold-stimulus headache; complicated migraine; drug withdrawal headache; exertional headache; external compression headache; familial hemiplegic migraine; familiar hemiplegic migraine; frequent headaches; headache; headache histamine; headache nos; headache nos aggravated; headache postoperative; hemicephalgia; hemiplegic migraine; lumbar puncture headache; medication overuse headache; migraine; migraine aggravated; migraine hemiplegic; migraine nos; migraine with aura; migraine without aura; new daily persistent headache; occipital neuralgia; ophthalmoplegic migraine; post lumbar puncture syndrome; post myelography headache; post procedural headache; post-traumatic headache; premenstrual headache; primary cough headache; primary headache associated with sexual activity; procedural headache; reaction to spinal or lumbar puncture; retinal migraine; sinus headache; status migrainosus; sunct syndrome; tension headache; tension headaches;

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thunderclap headache; vascular headache; vestibular migraine; and vogt-koyanagi-harada disease

Headache Fda B MQG

Basilar migraine; cervicogenic headache; chronic paroxysmal hemicrania; cluster headache; cluster headaches; cold-stimulus headache; complicated migraine; drug withdrawal headache; exertional headache; external compression headache; familial hemiplegic migraine; familial hemiplegic migraine; frequent headaches; head discomfort; headache; headache histamine; headache nos; headache nos aggravated; headache postoperative; hemicephalalgia; hemiplegic migraine; lumbar puncture headache; medication overuse headache; migraine; migraine aggravated; migraine hemiplegic; migraine nos; migraine prophylaxis; migraine with aura; migraine without aura; new daily persistent headache; occipital neuralgia; ophthalmoplegic migraine; post lumbar puncture syndrome; post myelography headache; post procedural headache; post-traumatic headache; premenstrual headache; primary cough headache; primary headache associated with sexual activity; procedural headache; reaction to spinal or lumbar puncture; retinal migraine; sinus headache; status migrainosus; sunct syndrome; tension headache; tension headaches; thunderclap headache; vascular headache; vestibular migraine; and vogt-koyanagi-harada disease

Headache MQG

Cluster headache; complicated migraine; exertional headache; headache; medication overuse headache; migraine; migraine with aura; migraine without aura; post lumbar puncture syndrome; post procedural headache; post-traumatic headache; primary cough headache; procedural headache; sinus headache; status migrainosus; tension headache; vascular headache; and vestibular migraine

Hemorrhage Fda N MQG

Abdominal aortic aneurysm hemorrhage; abdominal hematoma; abdominal wall hematoma; abdominal wall hemorrhage; acute hemorrhagic leukoencephalitis; acute hemorrhagic ulcerative colitis; administration site bruise; administration site hematoma; administration site hemorrhage; adrenal hematoma; adrenal hemorrhage; anal fissure hemorrhage; anal hemorrhage; anal ulcer hemorrhage; anastomotic hemorrhage; anastomotic ulcer hemorrhage; anastomotic ulcer hemorrhage, obstructive; aneurysm ruptured; anorectal varices hemorrhage; antepartum hemorrhage; aortic aneurysm rupture; aortic annulus rupture; aortic dissection rupture; aortic intramural hematoma; aortic perforation; aortic rupture; aortoenteric fistula; aponeurosis contusion; application site bleeding; application site bruise; application site bruising; application site hematoma; application site hemorrhage; application site purpura; arterial hemorrhage; arterial hemorrhage nos; arterial intramural hematoma; arterial perforation; arterial rupture; arterial rupture nos; arteriovenous fistula site hematoma; arteriovenous fistula site hemorrhage; arteriovenous graft site hematoma; arteriovenous graft site hemorrhage; atrial rupture; auricular hematoma; basal ganglia hematoma; basal ganglia

hemorrhage; basilar artery perforation; battle's sign; benign familial hematuria; biliary-vascular fistula; bladder tamponade; bladder thrombotic tamponade; bleeding peripartum; bleeding tendency; bleeding varicose vein; blood blister; blood in stool; blood loss anemia; blood urine; blood urine present; bloody airway discharge; bloody discharge; bloody drainage; bloody peritoneal effluent; bone contusion; bone marrow hemorrhage; brain contusion; brain stem hematoma; brain stem hemorrhage; brain stem microhemorrhage; breast hematoma; breast hemorrhage; broad ligament hematoma; bronchial hemorrhage; bronchial varices hemorrhage; bursal hematoma; cardiac contusion; carotid aneurysm rupture; carotid artery perforation; catheter site bruise; catheter site ecchymosis; catheter site hematoma; catheter site hemorrhage; central nervous system hemorrhage; cephalhematoma; cerebellar hematoma; cerebellar hematoma nos; cerebellar hemorrhage; cerebellar microhemorrhage; cerebral aneurysm perforation; cerebral aneurysm ruptured syphilitic; cerebral arteriovenous malformation hemorrhagic; cerebral artery perforation; cerebral cyst hemorrhage; cerebral hematoma; cerebral hemorrhage; cerebral hemorrhage fetal; cerebral hemorrhage neonatal; cerebral microhemorrhage; cervix hematoma uterine; cervix hemorrhage uterine; chest wall hematoma; choroidal hematoma; choroidal hemorrhage; chronic gastrointestinal bleeding; chronic pigmented purpura; ciliary body hemorrhage; clotted hemothorax; coital bleeding; colitis hemorrhagic; colonic hematoma; colonic hemorrhage; conjunctival hemorrhage; contusion; contusion pulmonary; corneal bleeding; coronary artery atheroma hemorrhage; cullen's sign; cystitis hemorrhagic; deep dissecting hematoma; diarrheahemorrhagic; diverticulitis intestinal hemorrhagic; diverticulum intestinal hemorrhagic; duodenal hemorrhage; duodenal ulcer hemorrhage; duodenal ulcer hemorrhage, obstructive; duodenitis hemorrhagic; dysfunctional uterine bleeding; ear hemorrhage; ecchymosis; encephalitis hemorrhagic; enteritis hemorrhagic; enterocolitis hemorrhagic; epidural hemorrhage; epistaxis; exsanguination; extra-axial hemorrhage; extradural hematoma; extraischemic cerebral hematoma; extravasation blood; eye contusion; eye hematoma; eye hemorrhage; eye hemorrhage nos; eyelid bleeding; eyelid contusion; eyelid hematoma; eyelid hemorrhage; femoral artery perforation; femoral vein perforation; gardner-diamond syndrome; gastric hemorrhage; gastric mucosal hypertrophy, hemorrhagic; gastric ulcer hemorrhage; gastric ulcer hemorrhage, obstructive; gastric varices hemorrhage; gastritis alcoholic hemorrhagic; gastritis atrophic hemorrhagic; gastritis hemorrhagic; gastritis hemorrhagic aggravated; gastroduodenal hemorrhage; gastroduodenitis hemorrhagic; gastrointestinal angiodysplasia hemorrhagic; gastrointestinal hemorrhage; gastrointestinal hemorrhage nos; gastrointestinal organ contusion; gastrointestinal polyp hemorrhage; gastrointestinal ulcer hemorrhage; gastrointestinal vascular malformation hemorrhagic; genital contusion; genital hemorrhage; genital hemorrhage nos; gingival bleeding; graft hemorrhage; grey turner's sign; hemarthrosis; hematemesis; hematidrosis; hematochezia; hematocoele; hematoma; hematoma infection; hematoma nos; hematomyelia; hematosalpinx; hematospermia; hematotympanum; hematuria; hematuria aggravated; hematuria traumatic; hemobilia; hemopericardium; hemoperitoneum; hemophilic pseudotumor; hemoptysis; hemorrhage; hemorrhage coronary artery; hemorrhage fetal; hemorrhage in pregnancy; hemorrhage into ovarian cyst; hemorrhage intracranial;

hemorrhage neonatal; hemorrhage nos; hemorrhage nos aggravated; hemorrhage nos fetal; hemorrhage nos neonatal; hemorrhage subcutaneous; hemorrhage subepidermal; hemorrhage urinary tract; hemorrhagic adrenal infarction; hemorrhagic anemia; hemorrhagic arteriovenous malformation; hemorrhagic ascites; hemorrhagic breast cyst; hemorrhagic cerebral infarction; hemorrhagic cholecystitis; hemorrhagic cyst; hemorrhagic diathesis; hemorrhagic disease of newborn; hemorrhagic disorder; hemorrhagic erosive gastritis; hemorrhagic hepatic cyst; hemorrhagic infarction; hemorrhagic necrotic pancreatitis; hemorrhagic ovarian cyst; hemorrhagic pneumonia; hemorrhagic stroke; hemorrhagic thyroid cyst; hemorrhagic transformation stroke; hemorrhagic tumornecrosis; hemorrhagic urticaria; hemorrhagic varicella syndrome; hemorrhagic vasculitis; hemorrhoidal hemorrhage; hemothorax; hemorrhagic tumornecrosis; hemorrhoidal bleeding; henoch-schonlein purpura; henoch-schonlein purpura nephritis; hepatic hemangioma rupture; hepatic hematoma; hepatic hemorrhage; hereditary hemorrhagic telangiectasia; hereditary renal microhematuria; hyperfibrinolysis; hyphema; idiopathic purpura; ileal hemorrhage; iliac artery perforation; iliac artery rupture; iliac vein perforation; implant site bruising; implant site hematoma; implant site hemorrhage; incision site hematoma; incision site hemorrhage; induced abortion hemorrhage; inferior vena cava perforation; infusion site bruising; infusion site hematoma; infusion site hemorrhage; injection site bruising; injection site hematoma; injection site hemorrhage; instillation site bruise; instillation site hematoma; instillation site hemorrhage; intermenstrual bleeding; internal hemorrhage; intestinal hematoma; intestinal hemorrhage; intestinal polyp hemorrhage; intestinal stoma site bleeding; intestinal varices hemorrhage; intra-abdominal hematoma; intra-abdominal hemorrhage; intra-abdominal hemorrhage nos; intracerebral hematoma evacuation; intracerebral hematoma evacuation nos; intracranial epidural hematoma; intracranial hematoma; intracranial hemorrhage nos; intracranial tumorhemorrhage; intraocular hematoma; intraoperative hemorrhage; intrapartum hemorrhage; intraventricular hemorrhage; intraventricular hemorrhage neonatal; intraventricular hemorrhage nos; iris hemorrhage; jejunal hemorrhage; joint microhemorrhage; kidney contusion; lacrimal hemorrhage; large intestinal hemorrhage; large intestinal ulcer hemorrhage; large intestinal ulcer nos hemorrhage; laryngeal hematoma; laryngeal hemorrhage; lip hematoma; lip hemorrhage; liver contusion; loin pain hematuria syndrome; lower gastrointestinal hemorrhage; lower limb artery perforation; lymph node hemorrhage; majocchi's purpura; mallory-weiss syndrome; maxillary sinus hematoma; mediastinal hematoma; mediastinal hemorrhage; medical device site bruise; medical device site hematoma; medical device site hemorrhage; melaena; melaena neonatal; meningorrhagia; menometrorrhagia; menorrhagia; mesenteric hematoma; mesenteric hemorrhage; metrorrhagia; mouth hemorrhage; mucocutaneous hemorrhage; mucosal hemorrhage; mucosal hemorrhage nos; muscle contusion; muscle hemorrhage; myocardial hemorrhage; myocardial rupture; naevus hemorrhage; nail bed bleeding; nasal septum hematoma; neonatal gastrointestinal hemorrhage; nephritis hemorrhagic; nipple exudate bloody; ocular retrobulbar hemorrhage; esophageal hemorrhage; esophageal intramural hematoma; esophageal ulcer hemorrhage; esophageal varices hemorrhage; esophagitis hemorrhagic; operative hemorrhage;

optic disc hemorrhage; optic nerve sheath hemorrhage; oral contusion; oral mucosa hematoma; oral mucosal petechiae; osteorrhagia; ovarian hematoma; ovarian hemorrhage; palpable purpura; pancreatic contusion; pancreatic hemorrhage; pancreatitis hemorrhagic; papillary muscle hemorrhage; paranasal sinus hematoma; paranasal sinus hemorrhage; parathyroid hemorrhage; parotid gland hemorrhage; pelvic hematoma; pelvic hematoma obstetric; pelvic hemorrhage; penile contusion; penile hematoma; penile hemorrhage; peptic ulcer hemorrhage; peptic ulcer hemorrhage, obstructive; perforation of great vessels; pericardial hemorrhage; perineal hematoma; periorbital contusion; periorbital hematoma; periorbital hemorrhage; periosteal hematoma; peripartum hemorrhage; peripheral artery aneurysm rupture; peripheral artery hematoma; perirenal hematoma; peritoneal effusion bloody; peritoneal hematoma; peritoneal hemorrhage; periventricular hemorrhage neonatal; petechiae; pharyngeal hematoma; pharyngeal hemorrhage; pituitary hemorrhage; placenta praevia hemorrhage; pleural hemorrhage; polymenorrhagia; post abortion hemorrhage; post coital bleeding; post procedural contusion; post procedural hematoma; post procedural hematuria; post procedural hemorrhage; post transfusion purpura; post-menopausal bleeding; postmenopausal hemorrhage; postoperative bruise; postoperative hematoma; post-operative hemorrhage; postpartum hemorrhage; post-partum hemorrhage; post-traumatic punctate intraepidermal hemorrhage; premature separation of placenta; procedural hemorrhage; proctitis hemorrhagic; prostatic hemorrhage; pulmonary alveolar hemorrhage; pulmonary contusion; pulmonary hematoma; pulmonary hemorrhage; pulmonary hemorrhage neonatal; puncture site bruise; puncture site hematoma; puncture site hemorrhage; purpura; purpura cerebri; purpura fulminans; purpura neonatal; purpura nonthrombocytopenic; purpura non-thrombocytopenic; purpura nos; purpura senile; putamen hemorrhage; radiation associated hemorrhage; rectal bleeding; rectal hemorrhage; rectal ulcer hemorrhage; renal artery perforation; renal cyst hemorrhage; renal hematoma; renal hemorrhage; respiratory tract hemorrhage; respiratory tract hemorrhage neonatal; respiratory tract hemorrhage nos; retinal aneurysm rupture; retinal bleeding; retinal hemorrhage; retinopathy hemorrhagic; retroperitoneal hematoma; retroperitoneal hemorrhage; retroplacental hematoma; ruptured cerebral aneurysm; schamberg's disease; scleral hemorrhage; scrotal hematocele; scrotal hematoma; shock hemorrhagic; skin bleeding; skin hemorrhage; skin neoplasm bleeding; skin ulcer hemorrhage; small intestinal hemorrhage; small intestinal ulcer hemorrhage; small intestinal ulcer nos hemorrhage; soft tissue hemorrhage; spermatic cord hemorrhage; spinal cord hematoma; spinal cord hemorrhage; spinal epidural hematoma; spinal epidural hemorrhage; spinal hematoma; spinal subarachnoid hemorrhage; spinal subdural hematoma; spinal subdural hemorrhage; spleen contusion; splenic artery perforation; splenic hematoma; splenic hemorrhage; splenic varices hemorrhage; splinter hemorrhages; spontaneous hematoma; spontaneous hemorrhage; spontaneous hyphema; stoma site hemorrhage; stomatitis hemorrhagic; subarachnoid hematoma; subarachnoid hemorrhage; subarachnoid hemorrhage nos; subchorionic hematoma; subchorionic hemorrhage; subcutaneous hematoma; subdural hematoma; subendocardial hemorrhage; subgaleal hematoma; subgaleal hemorrhage; subretinal hematoma; thrombocytopenic purpura; thrombotic thrombocytopenic

purpura; tongue hematoma; tooth pulp hemorrhage; traumatic hematoma; traumatic intracranial hematoma; umbilical hematoma; urinary occult blood positive; urticaria hemorrhagica; uterine hematoma; vaccination site bruising; vaccination site hematoma; vaccination site hemorrhage; vaginal hematoma; vaginal hemorrhage; vascular access site bruising; vascular access site contusion; vascular access site hematoma; vascular access site hemorrhage; vascular graft hemorrhage; vascular purpura; vessel puncture site bruise; vessel puncture site hematoma; vitreous hematoma; vulval hematoma; withdrawal bleeding irregular; and wound hematoma

Hypotension Fda N MQG

Arterial pressure nos decreased; blood pressure decreased; blood pressure diastolic decreased; blood pressure systolic decreased; diastolic hypotension; hypotension; hypotension aggravated; hypotension nos; hypotension on induction; hypotension postural aggravated; hypotensive anaesthesia procedure; hypotensive transfusion reaction; intraoperative hypotension; neonatal hypotension; orthostatic hypotension; postoperative hypotension; postural hypotension; and procedural hypotension

Infection MQG

Abdominal abscess; abdominal hernia infection; abdominal infection; abdominal wall abscess; abdominal wall infection; abortion infected; abscess; abscess bacterial; abscess drainage; abscess fungal; abscess intestinal; abscess jaw; abscess limb; abscess neck; abscess of external auditory meatus; abscess of eyelid; abscess of salivary gland; abscess oral; abscess rupture; abscess soft tissue; abscess sweat gland; acanthamoeba infection; acanthamoeba keratitis; acarasis; acid fast bacilli infection; acinetobacter bacteremia; acinetobacter infection; acquired immunodeficiency syndrome; actinomycosis; actinomycotic abdominal infection; actinomycotic pulmonary infection; actinomycotic skin infection; acute diverticulitis; acute endocarditis; acute hepatitis b; acute hepatitis c; acute postoperative sialadenitis; acute pulmonary histoplasmosis; acute sinusitis; acute tonsillitis; adenoiditis; adenoviral conjunctivitis; adenoviral hemorrhagic cystitis; adenoviral hepatitis; adenoviral upper respiratory infection; adenovirus infection; administration site cellulitis; administration site infection; administration site joint infection; adrenal gland tuberculosis; aeromonas infection; african trypanosomiasis; alcaligenes infection; american trypanosomiasis; amoebiasis; anal abscess; anal candidiasis; anal fistula infection; anal fungal infection; anorectal human papilloma virus infection; anorectal infection; appendiceal abscess; appendicitis; appendicitis perforated; application site infection; arteriovenous fistula site infection; arteriovenous graft site abscess; arteriovenous graft site infection; arthritis bacterial; arthritis fungal; arthritis infective; ascariasis; ascites infection; aspergilloma; aspergillosis; atypical mycobacterial infection; atypical mycobacterial lymphadenitis; atypical mycobacterial pneumonia; atypical pneumonia; avian influenza; axillary candidiasis; babesiosis; bacteremia; bacterial diarrhea; bacterial infection; bacterial prostatitis; bacterial pyelonephritis; bacterial rhinitis; bacterial sepsis; bacterial tracheitis; bacterial

vaginosis; bacteroides bacteremia; balanitis candida; bartholin's abscess; beta hemolytic streptococcal infection; biliary sepsis; biliary tract infection fungal; bladder candidiasis; blastocystis infection; blister infected; blood culture positive; body tinea; borrelia infection; brain abscess; breast abscess; breast cellulitis; bronchial infection; bronchiolitis; bronchitis; bronchitis acute; bronchitis acute viral; bronchitis bacterial; bronchitis fungal; bronchitis pneumococcal; bronchitis viral; bronchopneumonia; bronchopulmonary aspergillosis; bronchopulmonary aspergillosis allergic; bullous impetigo; burn infection; bursitis infective; bursitis infective staphylococcal; campylobacter gastroenteritis; campylobacter infection; campylobacter intestinal infection; candida infection; candida pneumonia; candida sepsis; candidiasis; candiduria; carbuncle; cardiac infection; catheter related infection; catheter site abscess; catheter site infection; cellulitis; cellulitis gangrenous; cellulitis laryngeal; cellulitis of male external genital organ; cellulitis orbital; cellulitis staphylococcal; cellulitis streptococcal central line infection; central nervous system fungal infection; central nervous system infection; cerebral fungal infection; cerebral toxoplasmosis; cervicitis; cervicitis streptococcal; ; chest wall abscess; chikungunya virus infection; chlamydial infection; cholangitis cholangitis acute; cholangitis suppurative; cholecystitis; cholecystitis acute; cholecystitis chronic; cholecystitis infective; cholecystocholangitis; chronic sinusitis; chronic tonsillitis; citrobacter infection; citrobacter sepsis; clostridial infection; clostridium colitis; clostridium difficile colitis; clostridium difficile infection; clostridium difficile sepsis; coccidioidomycosis; colonic abscess; community acquired infection; conjunctivitis bacterial; conjunctivitis infective; conjunctivitis viral; coxsackie viral infection; creutzfeldt-jakob disease; croup infectious; culture urine positive; culture wound positive; cutaneous tuberculosis; cystitis; cystitis bacterial; cystitis escherichia; cystitis klebsiella; cystitis pseudomonal; cystitis viral; cytomegalovirus colitis; cytomegalovirus hepatitis; cytomegalovirus infection; cytomegalovirus test positive; dacryocystitis; dacryocystitis infective; dengue fever; dental gangrene; dermatitis infected; dermatophytosis; dermatophytosis of nail; device related infection; device related sepsis; diabetic foot infection; diabetic gangrene; diarrhea infectious; disseminated tuberculosis; diverticulitis; diverticulitis intestinal hemorrhagic; douglas' abscess; ear infection; ear infection bacterial; ear infection fungal; ear infection viral; ear lobe infection; echinococcosis; ecthyma; eczema impetiginous; eczema infected; emphysematous cholecystitis; empyema; encephalitis fungal; encephalitis herpes; encephalitis viral; endocarditis; endocarditis bacterial; endocarditis enterococcal; endocarditis gonococcal; endocarditis hemophilus; endocarditis helminthic; endocarditis histoplasma; endocarditis meningococcal; endocarditis pseudomonal; endocarditis staphylococcal; endocarditis syphilitic; endocarditis viral; endophthalmitis; enteritis infectious; enterobacter bacteremia; enterobacter infection; enterobacter sepsis; enterobiasis; enterococcal bacteremia; enterococcal infection; enterococcal sepsis; enterocolitis bacterial; enterocolitis fungal; enterocolitis hemorrhagic; enterocolitis infectious; enterocolitis viral; enterovirus infection; epidemic nephropathy; epidemic polyarthritis; epiglottitis; epstein-barr virus infection; erysipelas; erythrasma; escherichia bacteremia; escherichia infection; escherichia pyelonephritis; escherichia sepsis; escherichia urinary tract infection; external ear cellulitis; extradural abscess; eye abscess; eye infection; eye infection bacterial; eye infection

fungal; eye infection staphylococcal; eye infection viral; eyelid boil; eyelid infection; fasciolopsiasis; febrile infection; folliculitis; fungemia; fungal abscess central nervous system; fungal balanitis; fungal cystitis; fungal endocarditis; fungal infection; fungal labyrinthitis; fungal esophagitis; fungal paronychia; fungal peritonitis; fungal pharyngitis; fungal rash; fungal retinitis; fungal rhinitis; fungal sepsis; fungal skin infection; fungal tracheitis; furuncle gallbladder empyema; gangrene; gardnerella infection; gas gangrene; gastric infection; gastric ulcer helicobacter; gastritis bacterial; gastritis fungal; gastritis viral; gastroenteritis; gastroenteritis adenovirus; gastroenteritis aeromonas; gastroenteritis bacterial; gastroenteritis clostridial; gastroenteritis cryptosporidial; gastroenteritis enteroviral; gastroenteritis escherichia coli; gastroenteritis norovirus; gastroenteritis norwalk virus; gastroenteritis rotavirus; gastroenteritis salmonella; gastroenteritis viral; gastrointestinal bacterial infection; gastrointestinal candidiasis; gastrointestinal fungal infection; gastrointestinal infection; gastrointestinal viral infection; genital abscess; genital candidiasis; genital herpes; genital infection; genital infection bacterial; genital infection female; genital infection fungal; genital infection male; genitourinary chlamydia infection; genitourinary tract infection; giardiasis; gingival abscess; gingival infection; gonorrhoea; graft infection; groin abscess; groin infection; h1n1 influenza; hematoma infection; hemophilus infection; hemorrhoid infection; helicobacter gastritis; helicobacter infection; helminthic infection; hepatic cyst infection; hepatic infection fungal; hepatitis a, hepatitis b; hepatitis c; hepatitis chronic active; hepatitis chronic persistent; hepatitis infectious; hepatitis viral; herpangina; herpes dermatitis; herpes esophagitis; herpes ophthalmic; herpes simplex; herpes simplex meningoencephalitis; herpes simplex ophthalmic; herpes virus infection; herpes zoster; herpes zoster ophthalmic; herpes zoster oticus; herpetic stomatitis; hiv infection; hookworm infection; hordeolum; hydrocele male infected; impetigo; implant site abscess; implant site infection; incision site abscess; incision site cellulitis; incision site infection; infected bite; infected bites; infected cyst; infected dermal cyst; infected epidermal cyst; infected fistula; infected naevus; infected sebaceous cyst; infected seroma; infected skin ulcer; infected varicose vein; infection; infection parasitic; infectious colitis; infectious mononucleosis; infectious peritonitis; infectious pleural effusion; infective exacerbation of bronchiectasis; infective exacerbation of chronic obstructive airways disease; infective glossitis; infective myositis; infective tenosynovitis; infective thrombosis; infective uveitis; influenza; influenza like illness; infusion site cellulitis; infusion site infection; injection site abscess; injection site cellulitis; injection site infection; intertrigo candida; intervertebral discitis; joint abscess; kaposi's varicelliform eruption; keratitis fungal; keratitis herpetic; keratitis viral; kidney infection; klebsiella bacteremia; klebsiella infection; klebsiella sepsis; labyrinthitis; laryngitis; laryngitis bacterial; laryngitis fungal; laryngitis viral; latent tuberculosis; legionella infection; leishmaniasis; lice infestation; lip infection; listeria sepsis; liver abscess; lobar pneumonia; localised infection; loeffler's syndrome; lower respiratory tract infection; lower respiratory tract infection bacterial; lower respiratory tract infection fungal; lower respiratory tract infection viral; lung abscess; lung infection; lung infection pseudomonal; lyme disease; lymph gland infection; lymph node abscess; lymph node tuberculosis; lymphadenitis fungal; lymphangitis; malaria; malarial myocarditis; mastitis; mastitis bacterial; mastitis fungal;

mastoiditis; mediastinitis; meningitis; meningitis aseptic; meningitis bacterial; meningitis fungal; meningitis herpes; meningitis listeria; meningitis meningococcal; meningitis pneumococcal; meningitis streptococcal; meningitis tuberculous; meningitis viral; meningococcal carditis; metapneumovirus infection; microsporidia infection; molluscum contagiosum; mononucleosis syndrome; moraxella infection; morganella infection; mucosal infection; mumps; murine typhus; muscle abscess; mycetoma mycotic; mycobacterial infection; mycobacterium abscessus infection; mycobacterium avium complex infection; mycoplasma infection; myocarditis meningococcal; myocarditis syphilitic; myocarditis toxoplasmal; myringitis; nail bed infection bacterial; nail bed infection fungal; nail infection; nail tinea; nasal abscess; nasopharyngitis; necrotising fasciitis; necrotising fasciitis fungal; nematodiasis; neuroborreliosis; neurocysticercosis; neutropenic sepsis; nipple infection; nosocomial infection; esophageal candidiasis; esophageal infection; omphalitis; onychomycosis; oophoritis; ophthalmic herpes simplex; ophthalmic herpes zoster; opisthorchiasis; oral bacterial infection; oral candidiasis; oral fungal infection; oral herpes; oral infection; oral viral infection; orchitis; organising pneumonia; oropharyngeal candidiasis; oropharyngitis fungal; osteomyelitis; osteomyelitis acute; osteomyelitis chronic; osteomyelitis fungal; otitis externa; otitis externa fungal; otitis media; otitis media acute; otitis media bacterial; otitis media chronic; otitis media fungal; otitis media viral; overgrowth bacterial; overgrowth fungal; pancreatic abscess; pancreatitis fungal; papilloma viral infection; parainfluenzae virus infection; paraesophageal abscess; parasitic gastroenteritis; parasitic infection intestinal; paraspinal abscess; paronychia; parotid abscess; parotitis; pasteurella infection; pelvic abscess; pelvic infection; pelvic inflammatory disease; penile abscess; penile infection; peptic ulcer helicobacter; perianal abscess; perianal fungal infection; pericarditis fungal; pericarditis gonococcal; pericarditis infective; pericarditis meningococcal; pericarditis mycoplasmal; pericarditis syphilitic; pericarditis tuberculous; perichondritis; peridiverticular abscess; perineal abscess; perineal infection; perinephric abscess; periodontal infection; periorbital cellulitis; perirectal abscess; peritoneal abscess; peritoneal infection; peritoneal tuberculosis; peritonitis; peritonitis bacterial; peritonsillar abscess; peritonsillitis; periumbilical abscess; pertussis; pharyngeal abscess; pharyngitis; pharyngitis bacterial; pharyngitis mycoplasmal; pharyngitis streptococcal; pharyngotonsillitis; phlebitis infective; pilonidal cyst; plasmodium falciparum infection; pneumococcal bacteremia; pneumococcal sepsis; pneumocystis jiroveci pneumonia; pneumocystis jirovecii pneumonia; pneumonia; pneumonia aspiration; pneumonia bacterial; pneumonia chlamydial; pneumonia cryptococcal; pneumonia cytomegaloviral; pneumonia fungal; pneumonia hemophilus; pneumonia herpes viral; pneumonia influenzal; pneumonia klebsiella; pneumonia legionella; pneumonia moraxella; pneumonia mycoplasmal; pneumonia necrotising; pneumonia pneumococcal; pneumonia primary atypical; pneumonia pseudomonal; pneumonia staphylococcal; pneumonia streptococcal; pneumonia viral; post procedural cellulitis; post procedural infection; post procedural pneumonia; post procedural sepsis; postoperative abscess; postoperative infection; postoperative wound infection; proctitis fungal; proctitis infectious; propionibacterium infection; prostate infection; proteus infection; pseudomembranous colitis; pseudomonal bacteremia; pseudomonal sepsis; pseudomonas

bronchitis; pseudomonas infection; psittacosis; psoas abscess; pulmonary mycosis; pulmonary sepsis; pulmonary tuberculoma; pulmonary tuberculosis; pulpitis dental; puncture site infection; pyelocystitis; pyelonephritis; pyelonephritis acute; pyelonephritis chronic; pyelonephritis fungal; pyoderma; pyoderma streptococcal; pyometra; pyonephrosis; pyopneumothorax; q fever; rash pustular; rectal abscess; renal cyst infection; renal tuberculosis; respiratory moniliasis; respiratory tract infection; respiratory tract infection bacterial; respiratory tract infection fungal; respiratory tract infection viral; retroperitoneal abscess; retroviral infection; rhinitis; rhinovirus infection; rocky mountain spotted fever; root canal infection; roseola; rotavirus infection; rubella; salmonella sepsis; salmonellosis; salpingitis; salpingo-oophoritis; scrotal abscess; scrotal infection; scrub typhus; sebaceous gland infection; sepsis; sepsis syndrome; septic arthritis staphylococcal; septic arthritis streptococcal; septic embolus; septic encephalopathy; septic necrosis; septic rash; septic shock; serratia infection; serratia sepsis; sexually transmitted disease; shigella infection; shunt infection; sialoadenitis; sinobronchitis; sinusitis; sinusitis bacterial; sinusitis fungal; skin bacterial infection; skin candida; skin infection; soft tissue infection; splenic abscess; splenic infection fungal; staphylococcal abscess; staphylococcal bacteremia; staphylococcal infection; staphylococcal osteomyelitis; staphylococcal pharyngitis; staphylococcal sepsis; staphylococcal skin infection; stenotrophomonas infection; stitch abscess; stoma site abscess; streptobacillus infection; streptococcal abscess; streptococcal bacteremia; streptococcal endocarditis; streptococcal infection; streptococcal sepsis; streptococcal urinary tract infection; strongyloidiasis; subacute endocarditis; subcutaneous abscess; subdiaphragmatic abscess; superinfection; superinfection fungal; superinfection lung; sycosis barbae; syphilis; syphilitic endocarditis of heart valve; systemic candida; systemic mycosis; taeniasis; testicular abscess; tick-borne viral encephalitis; tinea capitis; tinea cruris; tinea faciei; tinea infection; tinea manuum; tinea pedis; tinea versicolor; tongue abscess; tongue fungal infection; tonsillitis; tonsillitis bacterial; tonsillitis fungal; tonsillitis streptococcal; tooth abscess; tooth infection; toxic shock syndrome; toxoplasmosis; tracheitis; tracheobronchitis; tracheobronchitis viral; trachoma; trichophyton infection; trichophytosis; tropical eosinophilia; tuberculosis; tuberculosis of central nervous system; tuberculosis of genitourinary system; tuberculous pleurisy; typhoid fever; typhus; upper respiratory fungal infection; upper respiratory tract infection; upper respiratory tract infection bacterial; ureaplasma infection; ureteritis; urethritis; urethritis gonococcal; urinary bladder abscess; urinary tract infection; urinary tract infection bacterial; urinary tract infection enterococcal; urinary tract infection fungal; urinary tract infection pseudomonal; urinary tract infection staphylococcal; urinary tract infection viral; urogenital infection bacterial; urogenital infection fungal; urosepsis; uterine infection; vaginal abscess; vaginal candidiasis; vaginal infection; vaginal mycosis; vaginitis bacterial; vaginitis gardnerella; vancomycin-resistant enterococcal infection; varicella; viremia; viral cardiomyopathy; viral diarrhea; viral infection; viral labyrinthitis; viral myocarditis; viral pericarditis; viral pharyngitis; viral rash; viral rhinitis; viral sinusitis; viral skin infection; viral tracheitis; viral upper respiratory tract infection; vulval abscess; vulval cellulitis; vulvitis; vulvovaginal candidiasis; vulvovaginal mycotic infection; vulvovaginitis; vulvovaginitis

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gonococcal; vulvovaginitis trichomonal; west nile viral infection; wound abscess; wound infection; wound infection bacterial; wound infection fungal; wound infection pseudomonas; wound infection staphylococcal; wound sepsis; and yersinia infection

Infusion Site Reaction, Infusion Reaction MQG

Infusion site hematoma; infusion site hemorrhage; infusion site hyperesthesia; infusion site hypersensitivity; infusion site hypertrichosis; infusion site hypertrophy; infusion site hypoesthesia; infusion site induration; infusion site infection; infusion site inflammation; infusion site injury; infusion site irritation; infusion site ischemia; infusion site joint discomfort; infusion site joint effusion; infusion site joint erythema; infusion site joint infection; infusion site joint inflammation; infusion site joint movement impairment; infusion site joint pain; infusion site joint swelling; infusion site joint warmth; infusion site laceration; infusion site lymphadenopathy; infusion site macule; infusion site mass; infusion site mobility decreased; infusion site necrosis; infusion site nerve damage; infusion site nodule; infusion site edema; infusion site pain; infusion site pallor; infusion site papule; infusion site paresthesia; infusion site phlebitis; infusion site photosensitivity reaction; infusion site plaque; infusion site pruritus; infusion site pustule; infusion site rash; infusion site reaction; infusion site recall reaction; infusion site scab; infusion site scar; infusion site streaking; infusion site swelling; infusion site thrombosis; infusion site ulcer; infusion site urticaria; infusion site vasculitis; infusion site vesicles; and infusion site warmth

Intracranial Hemorrhage MQG

Basal ganglia hemorrhage; brain contusion; brain stem hemorrhage; cephalhematoma; cerebellar hematoma; cerebellar hemorrhage; cerebral hematoma; cerebral hemorrhage; cerebral hemorrhage traumatic; cerebral microhemorrhage; extradural hematoma; hemorrhage intracranial; hemorrhagic cerebral infarction; hemorrhagic stroke; intracranial hematoma; intraventricular hemorrhage; putamen hemorrhage; ruptured cerebral aneurysm; subarachnoid hemorrhage; subdural hematoma; subdural hemorrhage; subgaleal hematoma; thalamus hemorrhage; and traumatic intracranial hemorrhage

Irritability Fda N MQG

Agitated depression; agitation; agitation neonatal; agitation postoperative; frustration tolerance decreased; impatience; infant irritability; irritability; and terminal agitation

Local Administration Reactions Fda N MQG

Administration site dermatitis; administration site eczema; administration site hypersensitivity; administration site pain; administration site rash; administration site reaction neonatal; administration site recall reaction; administration site urticaria; administration site vasculitis; application site dermatitis; application site eczema; application site hypersensitivity; application site pain; application site rash; application site reaction; application site recall reaction; application site urticaria; application site vasculitis; catheter site dermatitis; catheter site

eczema; catheter site hypersensitivity; catheter site pain; catheter site rash; catheter site urticaria; catheter site vasculitis; implant site dermatitis; implant site hypersensitivity; implant site pain; implant site rash; implant site urticaria; incision site dermatitis; incision site discharge; incision site fibrosis; incision site impaired healing; incision site pain; incision site rash; infusion related reaction; infusion site abscess; infusion site abscess sterile; infusion site anaesthesia; infusion site atrophy; infusion site bruising; infusion site calcification; infusion site cellulitis; infusion site coldness; infusion site cyst; infusion site dermatitis; infusion site discharge; infusion site discoloration; infusion site discomfort; infusion site dryness; infusion site dysesthesia; infusion site eczema; infusion site erosion; infusion site erythema; infusion site eschar; infusion site exfoliation; infusion site extravasation; infusion site fibrosis; infusion site granuloma; infusion site hematoma; infusion site hemorrhage; infusion site hyperesthesia; infusion site hypersensitivity; infusion site hypertrichosis; infusion site hypertrophy; infusion site hypoesthesia; infusion site induration; infusion site inflammation; infusion site injury; infusion site irritation; infusion site ischemia; infusion site joint discomfort; infusion site joint effusion; infusion site joint erythema; infusion site joint movement impairment; infusion site joint pain; infusion site joint swelling; infusion site joint warmth; infusion site joint infection; infusion site joint inflammation; infusion site laceration; infusion site lymphadenopathy; infusion site macule; infusion site mass; infusion site mobility decreased; infusion site necrosis; infusion site nerve damage; infusion site nodule; infusion site edema; infusion site pain; infusion site pallor; infusion site papule; infusion site paresthesia; infusion site phlebitis; infusion site photosensitivity reaction; infusion site plaque; infusion site pustule; infusion site rash; infusion site reaction; infusion site recall reaction; infusion site scab; infusion site scar; infusion site streaking; infusion site swelling; infusion site thrombosis; infusion site ulcer; infusion site urticaria; infusion site vasculitis; infusion site warmth; infusion site infection; injection site abscess; injection site alopecia; injection site atrophy; injection site bruising; injection site cellulitis; injection site dermatitis; injection site discoloration; injection site discomfort; injection site eczema; injection site erythema; injection site extravasation; injection site hematoma; injection site hemorrhage; injection site hypersensitivity; injection site hypertrophy; injection site induration; injection site infection; injection site inflammation; injection site irritation; injection site macule; injection site mass; injection site necrosis; injection site nodule; injection site edema; injection site pain; injection site papule; injection site plaque; injection site pruritus; injection site rash; injection site reaction; injection site recall reaction; injection site scar; injection site swelling; injection site urticaria; injection site vasculitis; injection site vesicles; injection site warmth; instillation site hypersensitivity; instillation site pain; instillation site rash; instillation site urticaria; intra-ocular injection complication; medical device site dermatitis; medical device site eczema; medical device site hypersensitivity; medical device site pain; medical device site rash; medical device site recall reaction; medical device site urticaria; puncture site bruise; puncture site hematoma; puncture site pain; shoulder injury related to vaccine administration; vaccination site dermatitis; vaccination site eczema; vaccination site exfoliation; vaccination site hypersensitivity; vaccination site pain; vaccination site rash; vaccination site recall reaction; vaccination site

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urticaria; vaccination site vasculitis; vaccination site vesicles; vascular access site discharge; vascular access site pain; vascular access site vesicles; vessel puncture site pain; vessel puncture site rash; and vessel puncture site vesicles

Malignancy Fda N MQG

Abdominal wall neoplasm malignant; acinar cell carcinoma of pancreas; acinic cell carcinoma of salivary gland; acral lentiginous melanoma; acral lentiginous melanoma stage ii; acral lentiginous melanoma stage iii; acral lentiginous melanoma stage iv; acral lentiginous melanoma stage i; acute bilineal leukemia; acute biphenotypic leukemia; acute leukemia; acute lymphocytic leukemia; acute lymphocytic leukemia recurrent; acute lymphocytic leukemia refractory; acute megakaryocytic leukemia; acute monocytic leukemia; acute myeloid leukemia; acute myeloid leukemia recurrent; acute myeloid leukemia refractory; acute myelomonocytic leukemia; acute promyelocytic leukemia; acute undifferentiated leukemia; adenocarcinoma; adenocarcinoma gastric; adenocarcinoma of appendix; adenocarcinoma of colon; adenocarcinoma of salivary gland; adenocarcinoma of the cervix; adenocarcinoma pancreas; adenoid cystic carcinoma; adenoid cystic carcinoma of external auditory canal; adenoid cystic carcinoma of salivary gland; adenosquamous carcinoma of the cervix; adenosquamous carcinoma of vagina; adenosquamous cell carcinoma; adenosquamous cell lung cancer; adenosquamous cell lung cancer recurrent; adenosquamous cell lung cancer stage 0; adenosquamous cell lung cancer stage i; adenosquamous cell lung cancer stage ii; adenosquamous cell lung cancer stage iii; adenosquamous cell lung cancer stage iv; adrenal carcinoma; adrenal gland cancer; adrenal gland cancer metastatic; adrenocortical carcinoma; adult t-cell lymphoma/leukemia; adult t-cell lymphoma/leukemia recurrent; adult t-cell lymphoma/leukemia refractory; adult t-cell lymphoma/leukemia stage i; adult t-cell lymphoma/leukemia stage ii; adult t-cell lymphoma/leukemia stage iii; adult t-cell lymphoma/leukemia stage iv; esthesioneuroblastoma; aleukemic leukemia; anemia of malignant disease; anal cancer; anal cancer metastatic; anal cancer recurrent; anal cancer stage 0; anal cancer stage i; anal cancer stage ii; anal cancer stage iii; anal cancer stage iv; anal squamous cell carcinoma; anaplastic large cell lymphoma t- and null-cell types; anaplastic large cell lymphoma t- and null-cell types recurrent; anaplastic large cell lymphoma t- and null-cell types refractory; anaplastic large cell lymphoma t- and null-cell types stage i; anaplastic large cell lymphoma t- and null-cell types stage ii; anaplastic large cell lymphoma t- and null-cell types stage iii; anaplastic large cell lymphoma t- and null-cell types stage iv; anaplastic large-cell lymphoma; anaplastic thyroid cancer; angiocentric lymphoma; angiocentric lymphoma recurrent; angiocentric lymphoma refractory; angiocentric lymphoma stage i; angiocentric lymphoma stage ii; angiocentric lymphoma stage iii; angiocentric lymphoma stage iv; angioimmunoblastic t-cell lymphoma; angioimmunoblastic t-cell lymphoma recurrent; angioimmunoblastic t-cell lymphoma refractory; angioimmunoblastic t-cell lymphoma stage i; angioimmunoblastic t-cell lymphoma stage ii; angioimmunoblastic t-cell lymphoma stage iii; angioimmunoblastic t-cell lymphoma stage iv; angiosarcoma; angiosarcoma metastatic; apocrine breast carcinoma; appendix cancer; astrocytoma malignant; atypical

teratoid/rhabdoid tumor of CNS; b precursor type acute leukemia; basal cell carcinoma; basosquamous carcinoma; basosquamous carcinoma of skin; b-cell lymphoma; b-cell lymphoma recurrent; b-cell lymphoma refractory; b-cell lymphoma stage I; b-cell lymphoma stage II; b-cell lymphoma stage III; b-cell lymphoma stage IV; b-cell prolymphocytic leukemia; b-cell small lymphocytic lymphoma; b-cell small lymphocytic lymphoma recurrent; b-cell small lymphocytic lymphoma refractory; b-cell small lymphocytic lymphoma stage I; b-cell small lymphocytic lymphoma stage II; b-cell small lymphocytic lymphoma stage III; b-cell small lymphocytic lymphoma stage IV; b-cell type acute leukemia; b-cell unclassifiable lymphoma high grade; b-cell unclassifiable lymphoma low grade; bile duct adenocarcinoma; bile duct adenosquamous carcinoma; bile duct cancer; bile duct cancer recurrent; bile duct cancer stage 0; bile duct cancer stage I; bile duct cancer stage II; bile duct cancer stage III; bile duct cancer stage IV; bile duct squamous cell carcinoma; biliary cancer metastatic; Bing-Neel syndrome; bladder adenocarcinoma stage II; bladder adenocarcinoma stage III; bladder adenocarcinoma stage IV; bladder adenocarcinoma recurrent; bladder adenocarcinoma stage 0; bladder adenocarcinoma stage I; bladder adenocarcinoma stage unspecified; bladder cancer; bladder cancer recurrent; bladder cancer stage 0, with cancer in situ; bladder cancer stage 0, without cancer in situ; bladder cancer stage I, with cancer in situ; bladder cancer stage I, without cancer in situ; bladder cancer stage II; bladder cancer stage III; bladder cancer stage IV; bladder squamous cell carcinoma stage II; bladder squamous cell carcinoma stage III; bladder squamous cell carcinoma stage IV; bladder squamous cell carcinoma recurrent; bladder squamous cell carcinoma stage 0; bladder squamous cell carcinoma stage I; bladder squamous cell carcinoma stage unspecified; bladder transitional cell carcinoma; bladder transitional cell carcinoma stage II; bladder transitional cell carcinoma stage III; bladder transitional cell carcinoma stage IV; bladder transitional cell carcinoma metastatic; bladder transitional cell carcinoma recurrent; bladder transitional cell carcinoma stage 0; bladder transitional cell carcinoma stage I; blast crisis in myelogenous leukemia; bone cancer; bone cancer metastatic; bone giant cell tumor malignant; bone marrow leukemic cell infiltration; bone marrow tumor cell infiltration; bone neoplasm malignant; bone sarcoma; borderline ovarian tumor; borderline serous tumor of ovary; brain cancer metastatic; brain neoplasm malignant; breast cancer; breast cancer female; breast cancer in situ; breast cancer male; breast cancer metastatic; breast cancer recurrent; breast cancer stage I; breast cancer stage II; breast cancer stage III; breast cancer stage IV; breast implant-associated anaplastic large cell lymphoma; bronchial carcinoma; bronchioloalveolar carcinoma; Burkitt's leukemia; Burkitt's lymphoma; Burkitt's lymphoma recurrent; Burkitt's lymphoma refractory; Burkitt's lymphoma stage I; Burkitt's lymphoma stage II; Burkitt's lymphoma stage III; Burkitt's lymphoma stage IV; cancer fatigue; cancer pain; cancer staging; cancer surgery; carcinoid crisis; carcinoid heart disease; carcinoid syndrome; carcinoid tumor; carcinoid tumor of the cecum; carcinoid tumor of the duodenum; carcinoid tumor of the gastrointestinal tract; carcinoid tumor of the liver; carcinoid tumor of the ovary; carcinoid tumor of the pancreas; carcinoid tumor of the prostate; carcinoid tumor of the small bowel; carcinoid tumor of the stomach; carcinoid tumor pulmonary; carcinoma; carcinoma ex-pleomorphic adenoma; carcinoma in situ; carcinoma in situ of eye; carcinoma in

situ of penis; carcinoma in situ of skin; carcinoma in situ of trachea; carcinomatous polyarthritis; cardiac neoplasm malignant; cardiac neoplasm malignant nos; central nervous system leukemia; central nervous system lymphoma; cervix cancer metastatic; cervix carcinoma; cervix carcinoma recurrent; cervix carcinoma stage 0; cervix carcinoma stage I; cervix carcinoma stage ii; cervix carcinoma stage iii; cervix carcinoma stage iv; cervix neoplasm stage I; cervix neoplasm stage ii; cervix neoplasm stage iii; cervix neoplasm stage iv; cholangiocarcinoma; chondrosarcoma metastatic; choriocarcinoma; choroid plexus carcinoma; chromophobe renal cell carcinoma; chronic eosinophilic leukemia; chronic leukemia; chronic lymphocytic leukemia; chronic lymphocytic leukemia recurrent; chronic lymphocytic leukemia refractory; chronic lymphocytic leukemia stage 0; chronic lymphocytic leukemia stage 1; chronic lymphocytic leukemia stage 2; chronic lymphocytic leukemia stage 3; chronic lymphocytic leukemia stage 4; chronic lymphocytic leukemia transformation; chronic myeloid leukemia; chronic myeloid leukemia recurrent; chronic myeloid leukemia transformation; chronic myelomonocytic leukemia; ciliary body melanoma; clear cell carcinoma of cervix; clear cell carcinoma of the kidney; clear cell endometrial carcinoma; clear cell renal cell carcinoma; colon cancer; colon cancer metastatic; colon cancer recurrent; colon cancer stage 0; colon cancer stage I; colon cancer stage ii; colon cancer stage iii; colon cancer stage iv; colorectal adenocarcinoma; colorectal cancer; colorectal cancer metastatic; colorectal cancer recurrent; colorectal cancer stage I; colorectal cancer stage ii; colorectal cancer stage iii; colorectal cancer stage iv; colorectal carcinoma stage 0; composite lymphoma; congenital malignant neoplasm; cutaneous lymphoma; cystadenocarcinoma ovary; desmoplastic small round cell tumor; differentiation syndrome; diffuse large b-cell lymphoma; diffuse large b-cell lymphoma recurrent; diffuse large b-cell lymphoma refractory; diffuse large b-cell lymphoma stage I; diffuse large b-cell lymphoma stage ii; diffuse large b-cell lymphoma stage iii; diffuse large b-cell lymphoma stage iv; disseminated large cell lymphoma; double hit lymphoma; ductal adenocarcinoma of pancreas; ear neoplasm malignant; eccrine carcinoma; endocrine neoplasm malignant; endometrial adenocarcinoma; endometrial cancer; endometrial cancer metastatic; endometrial cancer recurrent; endometrial cancer stage 0; endometrial cancer stage I; endometrial cancer stage ii; endometrial cancer stage iii; endometrial cancer stage iv; enteropathy-associated t-cell lymphoma; eosinophilic leukemia; epididymal cancer; epiglottic carcinoma; epstein-barr virus associated lymphoma; erythroleukemia; ewing-like sarcoma; external ear neoplasm malignant; extragonadal primary embryonal carcinoma; extragonadal primary germ cell tumor; extragonadal primary germ cell tumor mixed; extragonadal primary germ cell tumor mixed stage I; extragonadal primary germ cell tumor mixed stage ii; extragonadal primary germ cell tumor mixed stage iii; extragonadal primary malignant teratoma; extranodal marginal zone b-cell lymphoma (balt type); extranodal marginal zone b-cell lymphoma (malt type); extranodal marginal zone b-cell lymphoma (malt type) recurrent; extranodal marginal zone b-cell lymphoma (malt type) refractory; extranodal marginal zone b-cell lymphoma (malt type) stage I; extranodal marginal zone b-cell lymphoma (malt type) stage ii; extranodal marginal zone b-cell lymphoma (malt type) stage iii; extranodal marginal zone b-cell lymphoma (malt type) stage iv; fallopian tube cancer; fallopian tube cancer metastatic; fallopian tube cancer stage I;

fallopian tube cancer stage ii; fallopian tube cancer stage iii; fallopian tube cancer stage iv; familial medullary thyroid cancer; female reproductive tract carcinoma in situ; follicle center lymphoma diffuse small cell lymphoma; follicle center lymphoma diffuse small cell lymphoma recurrent; follicle center lymphoma diffuse small cell lymphoma refractory; follicle center lymphoma diffuse small cell lymphoma stage I; follicle center lymphoma diffuse small cell lymphoma stage ii; follicle center lymphoma diffuse small cell lymphoma stage iii; follicle center lymphoma diffuse small cell lymphoma stage iv; follicle center lymphoma, follicular grade i, ii, iii; follicle center lymphoma, follicular grade i, ii, iii recurrent; follicle center lymphoma, follicular grade i, ii, iii refractory; follicle center lymphoma, follicular grade i, ii, iii stage i; follicle center lymphoma, follicular grade i, ii, iii stage ii; follicle center lymphoma, follicular grade i, ii, iii stage iii; follicle center lymphoma, follicular grade i, ii, iii stage iv; follicular thyroid cancer; gallbladder adenocarcinoma; gallbladder adenosquamous carcinoma; gallbladder cancer; gallbladder cancer metastatic; gallbladder cancer recurrent; gallbladder cancer stage 0; gallbladder cancer stage I; gallbladder cancer stage ii; gallbladder cancer stage iii; gallbladder cancer stage iv; gallbladder squamous cell carcinoma; gastric cancer; gastric cancer stage iv with metastases; gastric cancer recurrent; gastric cancer stage 0; gastric cancer stage I; gastric cancer stage ii; gastric cancer stage iii; gastric cancer stage iv; gastrinoma malignant; gastrointestinal adenocarcinoma; gastrointestinal cancer metastatic; gastrointestinal carcinoma; gastrointestinal carcinoma in situ; gastrointestinal lymphoma; gastrointestinal stromal cancer; gastrointestinal stromal tumor; gastrointestinal submucosal tumor; gastresophageal cancer; gastresophageal cancer recurrent; genital cancer male; genital cancer male in situ; genital neoplasm malignant female; germ cell cancer; germ cell cancer metastatic; gestational trophoblastic tumor; gingival cancer; glioblastoma multiforme; glioma; glioneuronal tumor; glottis carcinoma; granulosa cell tumor of the testis; hematological malignancy; hairy cell leukemia; hairy cell leukemia recurrent; head and neck cancer; head and neck cancer metastatic; head and neck cancer stage I; head and neck cancer stage ii; head and neck cancer stage iii; head and neck cancer stage iv; hepatic cancer; hepatic cancer metastatic; hepatic cancer recurrent; hepatic cancer stage I; hepatic cancer stage ii; hepatic cancer stage iii; hepatic cancer stage iv; hepatic neoplasm malignant; hepatic neoplasm malignant recurrent; hepatobiliary cancer; hepatobiliary cancer in situ; hepatocellular carcinoma; hepatosplenic t-cell lymphoma; her-2 positive breast cancer; her-2 positive gastric cancer; hereditary leiomyomatosis renal cell carcinoma; hereditary non-polyposis colorectal cancer syndrome; hereditary papillary renal carcinoma; hidradenocarcinoma; high grade b-cell lymphoma burkitt-like lymphoma; high grade b-cell lymphoma burkitt-like lymphoma recurrent; high grade b-cell lymphoma; burkitt-like lymphoma refractory; high grade b-cell lymphoma burkitt-like lymphoma stage I; high grade b-cell lymphoma burkitt-like lymphoma stage ii; high grade b-cell lymphoma burkitt-like lymphoma stage iii; high grade b-cell lymphoma burkitt-like lymphoma stage iv; high-grade b-cell lymphoma; hormone refractory breast cancer; hormone-dependent prostate cancer; hormone-refractory prostate cancer; hormone-secreting ovarian tumor; huerthle cell carcinoma; hypercalcemia of malignancy; hypopharyngeal cancer; hypopharyngeal cancer recurrent; hypopharyngeal cancer stage 0; hypopharyngeal cancer stage I;

hypopharyngeal cancer stage ii; hypopharyngeal cancer stage iii; hypopharyngeal cancer stage iv; iatrogenic metastasis; immunoblastic lymphoma; inflammatory carcinoma of breast stage iii; inflammatory carcinoma of breast stage iv; inflammatory carcinoma of breast recurrent; inflammatory carcinoma of the breast; inflammatory malignant fibrous histiocytoma; inflammatory myofibroblastic tumor; intestinal adenocarcinoma; intestinal metastasis; intestinal t-cell lymphoma recurrent; intestinal t-cell lymphoma refractory; intestinal t-cell lymphoma stage I; intestinal t-cell lymphoma stage ii; intestinal t-cell lymphoma stage iii; intestinal t-cell lymphoma stage iv; intracranial germ cell tumor; intracranial meningioma malignant; intraductal papillary-mucinous carcinoma of pancreas; intraocular melanoma; invasive breast carcinoma; invasive ductal breast carcinoma; invasive lobular breast carcinoma; invasive papillary breast carcinoma; iritic melanoma; juvenile chronic myelomonocytic leukemia; keratinizing squamous cell carcinoma of nasopharynx; large cell carcinoma of the respiratory tract stage unspecified; large cell lung cancer; large cell lung cancer metastatic; large cell lung cancer recurrent; large cell lung cancer stage 0; large cell lung cancer stage I; large cell lung cancer stage ii; large cell lung cancer stage iii; large cell lung cancer stage iv; large intestine carcinoma; laryngeal cancer; laryngeal cancer metastatic; laryngeal cancer recurrent; laryngeal cancer stage 0; laryngeal cancer stage I; laryngeal cancer stage ii; laryngeal cancer stage iii; laryngeal cancer stage iv; laryngeal squamous cell carcinoma; leiomyosarcoma; leiomyosarcoma metastatic; lentigo maligna; lentigo maligna recurrent; lentigo maligna stage I; lentigo maligna stage ii; lentigo maligna stage iii; lentigo maligna stage iv; leptomeningeal myelomatosis; leukemia; leukemia basophilic; leukemia cutis; leukemia granulocytic; leukemia monocytic; leukemia recurrent; leukemic cardiac infiltration; leukemic infiltration; leukemic infiltration extramedullary; leukemic infiltration gingiva; leukemic infiltration hepatic; leukemic infiltration ovary; leukemic infiltration pulmonary; leukemic infiltration renal; leukemic lymphoma; leukemic retinopathy; leydig cell tumor of the testis; lip and/or oral cavity cancer; lip and/or oral cavity cancer recurrent; lip and/or oral cavity cancer stage 0; lip and/or oral cavity cancer stage I; lip and/or oral cavity cancer stage ii; lip and/or oral cavity cancer stage iii; lip and/or oral cavity cancer stage iv; lip neoplasm malignant stage unspecified; lip squamous cell carcinoma; liposarcoma; liver carcinoma ruptured; lobular breast carcinoma in situ; lung adenocarcinoma; lung adenocarcinoma stage ii; lung adenocarcinoma stage iii; lung adenocarcinoma stage iv; lung adenocarcinoma metastatic; lung adenocarcinoma recurrent; lung adenocarcinoma stage 0; lung adenocarcinoma stage I; lung cancer metastatic; lung carcinoma cell type unspecified stage ii; lung carcinoma cell type unspecified stage iii; lung carcinoma cell type unspecified stage iv; lung carcinoma cell type unspecified recurrent; lung carcinoma cell type unspecified stage 0; lung carcinoma cell type unspecified stage I; lung infiltration malignant; lung neoplasm malignant; lung squamous cell carcinoma stage ii; lung squamous cell carcinoma stage iii; lung squamous cell carcinoma stage iv; lung squamous cell carcinoma metastatic; lung squamous cell carcinoma recurrent; lung squamous cell carcinoma stage 0; lung squamous cell carcinoma stage I; lung squamous cell carcinoma stage unspecified; lymphangiosis carcinomatosa; lymphocytic leukemia; lymphocytic lymphoma; lymphoma; lymphoma aids related; lymphoma operation; lymphomatoid papulosis; lymphoplasmacytoid;

ymphoma/immunocytoma; lymphoplasmacytoid lymphoma/immunocytoma recurrent; lymphoplasmacytoid lymphoma/immunocytoma refractory; lymphoplasmacytoid lymphoma/immunocytoma stage I; lymphoplasmacytoid lymphoma/immunocytoma stage ii; lymphoplasmacytoid lymphoma/immunocytoma stage iii; lymphoplasmacytoid lymphoma/immunocytoma stage iv; malignant anorectal neoplasm; malignant ascites; malignant biliary obstruction; malignant connective tissue neoplasm; malignant cranial nerve neoplasm; malignant fibrous histiocytoma; malignant gastrointestinal obstruction; malignant genitourinary tract neoplasm; malignant glioma; malignant joint neoplasm; malignant lymphoid neoplasm; malignant lymphoma unclassifiable high grade; malignant lymphoma unclassifiable low grade; malignant mast cell neoplasm; malignant mediastinal neoplasm; malignant melanoma; malignant melanoma in situ; malignant melanoma of eyelid; malignant melanoma of sites other than skin; malignant melanoma stage i; malignant melanoma stage ii; malignant melanoma stage iii; malignant melanoma stage iv; malignant meningioma metastatic; malignant mesenchymoma; malignant mesenchymoma metastatic; malignant mesenchymoma recurrent; malignant mesenteric neoplasm; malignant middle ear neoplasm; malignant muscle neoplasm; malignant neoplasm of ampulla of vater; malignant neoplasm of auricular cartilage; malignant neoplasm of choroid; malignant neoplasm of conjunctiva; malignant neoplasm of cornea; malignant neoplasm of eye; malignant neoplasm of eyelid; malignant neoplasm of islets of Langerhans; malignant neoplasm of lacrimal duct; malignant neoplasm of lacrimal gland; malignant neoplasm of orbit; malignant neoplasm of paraurethral glands; malignant neoplasm of placenta; malignant neoplasm of pleura; malignant neoplasm of pleura metastatic; malignant neoplasm of renal pelvis; malignant neoplasm of retina; malignant neoplasm of seminal vesicle; malignant neoplasm of spermatic cord; malignant neoplasm of spinal cord; malignant neoplasm of thorax; malignant neoplasm of thymus; malignant neoplasm of unknown primary site; malignant neoplasm of uterine adnexa; malignant neoplasm papilla of vater; malignant neoplasm progression; malignant nervous system neoplasm; malignant nipple neoplasm; malignant nipple neoplasm female; malignant nipple neoplasm male; malignant oligodendroglioma; malignant ovarian cyst; malignant palate neoplasm; malignant pericardial neoplasm; malignant peritoneal neoplasm; malignant pituitary tumor; malignant pleural effusion; malignant polyp; malignant respiratory tract neoplasm; malignant splenic neoplasm; malignant sweat gland neoplasm; malignant transformation; malignant tumorexcision; malignant urinary tract neoplasm; mantle cell lymphoma; mantle cell lymphoma recurrent; mantle cell lymphoma refractory; mantle cell lymphoma stage I; mantle cell lymphoma stage ii; mantle cell lymphoma stage iii; mantle cell lymphoma stage iv; marginal zone lymphoma; marginal zone lymphoma recurrent; marginal zone lymphoma refractory; marginal zone lymphoma stage I; marginal zone lymphoma stage ii; marginal zone lymphoma stage iii; marginal zone lymphoma stage iv; mastocytic leukemia; maternal cancer in pregnancy; mature b-cell type acute leukemia; medullary carcinoma of breast; medullary thyroid cancer; meningioma malignant; mesothelioma malignant; metaplastic breast carcinoma; metastases to bone; metastases to central nervous system; metastases to eye; metastases to gallbladder; metastases to heart; metastases to large intestine; metastases to liver; metastases to lung;

metastases to lymph nodes; metastases to pancreas; metastases to peritoneum; metastases to pleura; metastases to spine; metastasis; metastatic bronchial carcinoma; metastatic carcinoid tumor; metastatic carcinoma of the bladder; metastatic choriocarcinoma; metastatic gastric cancer; metastatic lymphoma; metastatic malignant melanoma; metastatic neoplasm; metastatic nervous system neoplasm; metastatic pain; metastatic renal cell carcinoma; metastatic salivary gland cancer; metastatic squamous cell carcinoma; metastatic uterine cancer; microsatellite instability cancer; minimal residual disease; mismatch repair cancer syndrome; mixed adenoneuroendocrine carcinoma; mixed hepatocellular cholangiocarcinoma; mucinous adenocarcinoma of appendix; mucinous breast carcinoma; mucinous cystadenocarcinoma of pancreas; mucinous cystadenocarcinoma ovary; mucinous endometrial carcinoma; mucoepidermoid carcinoma; mucoepidermoid carcinoma of salivary gland; mueller's mixed tumor; musculoskeletal cancer; myeloid leukemia; myeloma cast nephropathy; myelomalacia; myeloproliferative neoplasm; nasal cavity cancer; nasal sinus cancer; nasopharyngeal cancer; nasopharyngeal cancer metastatic; nasopharyngeal cancer recurrent; nasopharyngeal cancer stage 0; nasopharyngeal cancer stage I; nasopharyngeal cancer stage ii; nasopharyngeal cancer stage iii; nasopharyngeal cancer stage iv; natural killer-cell leukemia; natural killer-cell lymphoblastic lymphoma; neoplasm malignant; neoplasm of cornea unspecified malignancy; nephroblastoma; neuroendocrine breast tumor; neuroendocrine carcinoma; neuroendocrine carcinoma metastatic; neuroendocrine carcinoma of the bladder; neuroendocrine carcinoma of the skin; neuroendocrine tumor; neuroendocrine tumor of the lung; neuroendocrine tumor of the lung metastatic; nodal marginal zone b-cell lymphoma; nodal marginal zone b-cell lymphoma recurrent; nodal marginal zone b-cell lymphoma refractory; nodal marginal zone; b-cell lymphoma stage i; nodal marginal zone b-cell lymphoma stage ii; nodal marginal zone b-cell lymphoma stage iii; nodal marginal zone b-cell lymphoma stage iv; nodular lymphocyte predominant hodgkin lymphoma; nongerminomatous germ cell tumor of the CNS; non-hodgkin's lymphoma; non-hodgkin's lymphoma metastatic; non-hodgkin's lymphoma recurrent; non-hodgkin's lymphoma refractory; non-hodgkin's lymphoma stage I; non-hodgkin's lymphoma stage ii; non-hodgkin's lymphoma stage iii; non-hodgkin's lymphoma stage iv; non-hodgkin's lymphoma transformed recurrent; non-hodgkin's lymphoma unspecified histology aggressive; non-hodgkin's lymphoma unspecified histology aggressive recurrent; non-hodgkin's lymphoma unspecified histology aggressive refractory; non-hodgkin's lymphoma unspecified histology aggressive stage i; non-hodgkin's lymphoma unspecified histology aggressive stage ii; non-hodgkin's lymphoma unspecified histology aggressive stage iii; non-hodgkin's lymphoma unspecified histology aggressive stage iv; non-hodgkin's lymphoma unspecified histology indolent; non-hodgkin's lymphoma unspecified histology indolent stage I; non-hodgkin's lymphoma unspecified histology indolent stage ii; non-hodgkin's lymphoma unspecified histology indolent stage iii; non-hodgkin's lymphoma unspecified histology indolent stage iv; nonkeratinising carcinoma of nasopharynx; non-renal cell carcinoma of kidney; non-small cell lung cancer; non-small cell lung cancer metastatic; non-small cell lung cancer recurrent; non-small cell lung cancer stage 0; non-small cell lung cancer stage I; non-small cell lung cancer stage ii; non-small cell lung cancer stage iii; non-small cell lung cancer stage iiia;

non-small cell lung cancer stage iiib; non-small cell lung cancer stage iv; nut midline carcinoma; ocular cancer metastatic; ocular lymphoma; esophageal adenocarcinoma; esophageal adenocarcinoma stage ii; esophageal adenocarcinoma stage iii; esophageal adenocarcinoma stage iv; esophageal adenocarcinoma metastatic; esophageal adenocarcinoma recurrent; esophageal adenocarcinoma stage 0; esophageal adenocarcinoma stage I; esophageal cancer metastatic; esophageal carcinoma; esophageal carcinoma recurrent; esophageal carcinoma stage 0; esophageal squamous cell carcinoma; esophageal squamous cell carcinoma stage ii; esophageal squamous cell carcinoma stage iii; esophageal squamous cell carcinoma stage iv; esophageal squamous cell carcinoma metastatic; esophageal squamous cell carcinoma recurrent; esophageal squamous cell carcinoma stage 0; esophageal squamous cell carcinoma stage I; estrogen receptor positive breast cancer; oral cavity cancer metastatic; oropharyngeal cancer; oropharyngeal cancer recurrent; oropharyngeal cancer stage 0; oropharyngeal cancer stage I; oropharyngeal cancer stage ii; oropharyngeal cancer stage iii; oropharyngeal cancer stage iv; oropharyngeal cancer stage unspecified; oropharyngeal squamous cell carcinoma; osteosarcoma metastatic; otic cancer metastatic; ovarian cancer; ovarian cancer metastatic; ovarian cancer recurrent; ovarian cancer stage I; ovarian cancer stage ii; ovarian cancer stage iii; ovarian cancer stage iv; ovarian clear cell carcinoma; ovarian embryonal carcinoma; ovarian endometrioid carcinoma; ovarian epithelial cancer; ovarian epithelial cancer metastatic; ovarian epithelial cancer recurrent; ovarian epithelial cancer stage i; ovarian epithelial cancer stage ii; ovarian epithelial cancer stage iii; ovarian epithelial cancer stage iv; ovarian germ cell cancer; ovarian germ cell cancer stage I; ovarian germ cell cancer stage ii; ovarian germ cell cancer stage iii; ovarian germ cell cancer stage iv; ovarian germ cell choriocarcinoma; ovarian germ cell choriocarcinoma stage ii; ovarian germ cell choriocarcinoma stage iii; ovarian germ cell choriocarcinoma stage iv; ovarian germ cell choriocarcinoma stage i; ovarian germ cell embryonal carcinoma stage ii; ovarian germ cell embryonal carcinoma stage iii; ovarian germ cell embryonal carcinoma stage iv; ovarian germ cell embryonal carcinoma stage I; ovarian germ cell endodermal sinus tumor; ovarian germ cell endodermal sinus tumor stage I; ovarian germ cell endodermal sinus tumor stage ii; ovarian germ cell endodermal sinus tumor stage iii; ovarian germ cell endodermal sinus tumor stage iv; ovarian germ cell tumor; ovarian germ cell tumor mixed; ovarian granulosa cell tumor; ovarian granulosa-theca cell tumor; ovarian melanoma; ovarian sertoli-leydig cell tumor; ovarian stromal cancer; ovarian theca cell tumor; paget's disease of nipple; pancoast's tumor; pancreatic carcinoma; pancreatic carcinoma stage ii; pancreatic carcinoma stage iii; pancreatic carcinoma stage iv; pancreatic carcinoma metastatic; pancreatic carcinoma recurrent; pancreatic carcinoma stage 0; pancreatic carcinoma stage i; pancreatic neuroendocrine tumor; pancreatic neuroendocrine tumor metastatic; papillary cystadenoma lymphomatosum; papillary renal cell carcinoma; papillary serous endometrial carcinoma; papillary thyroid cancer; paracancerous pneumonia; paraganglion neoplasm malignant; paranasal sinus and nasal cavity malignant neoplasm; paranasal sinus and nasal cavity malignant neoplasm recurrent; paranasal sinus and nasal cavity malignant neoplasm stage 0; paranasal sinus and nasal cavity malignant neoplasm stage i; paranasal sinus and nasal cavity malignant neoplasm stage ii; paranasal sinus and nasal cavity

malignant neoplasm stage iii; paranasal sinus and nasal cavity malignant neoplasm stage iv; paraneoplastic arthritis; paraneoplastic dermatomyositis; paraneoplastic dermatosis; paraneoplastic encephalomyelitis; paraneoplastic glomerulonephritis; paraneoplastic hypoglycemia; paraneoplastic myelopathy; paraneoplastic nephrotic syndrome; paraneoplastic neurological syndrome; paraneoplastic pemphigus; paraneoplastic pleural effusion; paraneoplastic rash; paraneoplastic retinopathy; paraneoplastic syndrome; paraneoplastic thrombosis; parathyroid tumor malignant; penile cancer; penile squamous cell carcinoma; penis carcinoma; penis carcinoma stage ii; penis carcinoma stage iii; penis carcinoma stage iv; penis carcinoma metastatic; penis carcinoma recurrent; penis carcinoma stage i; pericardial effusion malignant; pericardial mesothelioma malignant; pericardial mesothelioma malignant recurrent; pericarditis malignant; peripheral primitive neuroectodermal bone tumor; peripheral primitive neuroectodermal tumor of soft tissue; peripheral t-cell lymphoma unspecified; peripheral t-cell lymphoma unspecified recurrent; peripheral t-cell lymphoma unspecified refractory; peripheral t-cell lymphoma unspecified stage i; peripheral t-cell lymphoma unspecified stage ii; peripheral t-cell lymphoma unspecified stage iii; peripheral t-cell lymphoma unspecified stage iv; peritoneal carcinoma metastatic; peritoneal mesothelioma malignant; peritoneal mesothelioma malignant recurrent; pheochromocytoma malignant; pharyngeal cancer; pharyngeal cancer metastatic; pharyngeal cancer recurrent; pharyngeal cancer stage 0; pharyngeal cancer stage I; pharyngeal cancer stage ii; pharyngeal cancer stage iii; pharyngeal cancer stage iv; pilomatrix carcinoma; pineal parenchymal neoplasm malignant; pituitary cancer metastatic; pituitary neoplasm malignant recurrent; plasma cell leukemia; plasma cell myeloma; plasma cell myeloma recurrent; plasma cell myeloma refractory; plasmablastic lymphoma; plasmacytoma; pleomorphic leiomyosarcoma; pleomorphic malignant fibrous histiocytoma; pleura carcinoma; pleural mesothelioma; pleural mesothelioma malignant; pleural mesothelioma malignant recurrent; pleuropulmonary blastoma; polyneuropathy in malignant disease; poorly differentiated thyroid carcinoma; porocarcinoma; postcricoid cancer; precursor b-lymphoblastic lymphoma; precursor b-lymphoblastic lymphoma recurrent; precursor b-lymphoblastic lymphoma refractory; precursor b-lymphoblastic lymphoma stage I; precursor b-lymphoblastic lymphoma stage ii; precursor b-lymphoblastic lymphoma stage iii; precursor b-lymphoblastic lymphoma stage iv; precursor t-lymphoblastic leukemia acute; precursor t-lymphoblastic lymphoma/leukemia; precursor t-lymphoblastic lymphoma/leukemia recurrent; precursor t-lymphoblastic lymphoma/leukemia refractory; precursor t-lymphoblastic lymphoma/leukemia stage i; precursor t-lymphoblastic lymphoma/leukemia stage ii; precursor t-lymphoblastic lymphoma/leukemia stage iii; precursor t-lymphoblastic lymphoma/leukemia stage iv; primary breast lymphoma; primary cardiac lymphoma; primary gastrointestinal follicular lymphoma; primary mediastinal large b-cell lymphoma; primary mediastinal large b-cell lymphoma recurrent; primary mediastinal large b-cell lymphoma refractory; primary mediastinal large b-cell lymphoma stage i; primary mediastinal large b-cell lymphoma stage ii; primary mediastinal large b-cell lymphoma stage iii; primary mediastinal large b-cell lymphoma stage iv; primary pulmonary melanoma; primitive neuroectodermal tumor; primitive neuroectodermal tumor metastatic; prolymphocytic leukemia; prostate cancer; prostate cancer

metastatic; prostate cancer recurrent; prostate cancer stage 0; prostate cancer stage i; prostate cancer stage ii; prostate cancer stage iii; prostate cancer stage iv; rectal adenocarcinoma; rectal cancer; rectal cancer metastatic; rectal cancer recurrent; rectal cancer stage 0; rectal cancer stage i; rectal cancer stage ii; rectal cancer stage iii; rectal cancer stage iv; rectosigmoid cancer; rectosigmoid cancer metastatic; rectosigmoid cancer recurrent; rectosigmoid cancer stage 0; rectosigmoid cancer stage i; rectosigmoid cancer stage ii; rectosigmoid cancer stage iii; rectosigmoid cancer stage iv; recurrent cancer; refractory cancer; renal cancer; renal cancer metastatic; renal cancer recurrent; renal cancer stage i; renal cancer stage ii; renal cancer stage iii; renal cancer stage iv; renal cell carcinoma; renal cell carcinoma stage ii; renal cell carcinoma stage iii; renal cell carcinoma stage iv; renal cell carcinoma recurrent; renal cell carcinoma stage i; renal cell carcinoma stage unspecified; respiratory tract carcinoma in situ; retroperitoneal cancer; retroperitoneal neoplasm metastatic; rhabdoid tumor; rhabdoid tumor of the kidney; salivary gland cancer; salivary gland cancer recurrent; salivary gland cancer stage 0; salivary gland cancer stage i; salivary gland cancer stage ii; salivary gland cancer stage iii; salivary gland cancer stage iv; sarcoma; sarcoma of skin; sarcoma uterus; sarcomatoid carcinoma; sarcomatoid carcinoma of the lung; sarcomatoid mesothelioma; scrotal cancer; sebaceous carcinoma; second primary malignancy; serous cystadenocarcinoma of pancreas; serous cystadenocarcinoma ovary; sertoli cell testicular tumor; signet-ring cell carcinoma; sinus cancer metastatic; skin cancer; skin cancer metastatic; skin carcinoma; skin squamous cell carcinoma metastatic; skin squamous cell carcinoma recurrent; small cell carcinoma; small cell carcinoma of the cervix; small cell lung cancer; small cell lung cancer extensive stage; small cell lung cancer limited stage; small cell lung cancer metastatic; small cell lung cancer recurrent; small cell lung cancer stage unspecified; small intestine adenocarcinoma; small intestine carcinoma; small intestine carcinoma stage ii; small intestine carcinoma stage iii; small intestine carcinoma stage iv; small intestine carcinoma metastatic; small intestine carcinoma recurrent; small intestine carcinoma stage 0; small intestine carcinoma stage i; solid pseudopapillary tumor of the pancreas; spinal meningioma malignant; splenic marginal zone lymphoma; splenic marginal zone lymphoma recurrent; splenic marginal zone lymphoma refractory; splenic marginal zone lymphoma stage i; splenic marginal zone lymphoma stage ii; splenic marginal zone lymphoma stage iii; splenic marginal zone lymphoma stage iv; splenic neoplasm malignancy unspecified; squamous cell breast carcinoma; squamous cell carcinoma; squamous cell carcinoma of head and neck; squamous cell carcinoma of lung; squamous cell carcinoma of pharynx; squamous cell carcinoma of skin; squamous cell carcinoma of the cervix; squamous cell carcinoma of the hypopharynx; squamous cell carcinoma of the oral cavity; squamous cell carcinoma of the parotid gland; squamous cell carcinoma of the tongue; squamous cell carcinoma of the vagina; squamous cell carcinoma of the vulva; squamous endometrial carcinoma; superficial spreading melanoma stage unspecified; targeted cancer therapy; t-cell chronic lymphocytic leukemia; t-cell lymphoma; t-cell lymphoma recurrent; t-cell lymphoma refractory; t-cell lymphoma stage i; t-cell lymphoma stage ii; t-cell lymphoma stage iii; t-cell lymphoma stage iv; t-cell prolymphocytic leukemia; t-cell type acute leukemia; t-cell unclassifiable lymphoma high grade; t-cell unclassifiable lymphoma low grade; testicular cancer

metastatic; testicular choriocarcinoma; testicular choriocarcinoma stage ii; testicular choriocarcinoma stage iii; testicular choriocarcinoma recurrent; testicular choriocarcinoma stage i; testicular embryonal carcinoma; testicular embryonal carcinoma stage ii; testicular embryonal carcinoma stage iii; testicular embryonal carcinoma stage i; testicular germ cell cancer; testicular germ cell cancer metastatic; testicular germ cell tumor; testicular germ cell tumor mixed; testicular germ cell tumor mixed incl choriocarcinoma stage i; testicular germ cell tumor mixed incl choriocarcinoma stage ii; testicular germ cell tumor mixed incl choriocarcinoma stage iii; testicular germ cell tumor mixed incl yolk sac tumor stage i; testicular germ cell tumor mixed incl yolk sac tumor stage ii; testicular germ cell tumor mixed stage i; testicular germ cell tumor mixed stage ii; testicular germ cell tumor mixed stage iii; testicular malignant teratoma; testicular malignant teratoma stage i; testicular malignant teratoma stage ii; testicular malignant teratoma stage iii; testicular yolk sac tumor; testicular yolk sac tumor stage i; testicular yolk sac tumor stage ii; testicular yolk sac tumor stage iii; testis cancer; testis cancer recurrent; throat cancer; thymic cancer metastatic; thymoma malignant; thymoma malignant recurrent; thyroid b-cell lymphoma; thyroid cancer; thyroid cancer metastatic; thyroid cancer recurrent; thyroid cancer stage 0; thyroid cancer stage i; thyroid cancer stage ii; thyroid cancer stage iii; thyroid cancer stage iv; tongue cancer metastatic; tongue cancer recurrent; tongue carcinoma stage ii; tongue carcinoma stage iii; tongue carcinoma stage iv; tongue carcinoma stage 0; tongue carcinoma stage i; tongue neoplasm malignant stage unspecified; tonsil cancer; tonsil cancer metastatic; tracheal cancer; transformation to acute myeloid leukemia; transitional cell cancer of renal pelvis and ureter metastatic; transitional cell cancer of the renal pelvis and ureter; transitional cell cancer of the renal pelvis and ureter localized; transitional cell cancer of the renal pelvis and ureter recurrent; transitional cell cancer of the renal pelvis and ureter regional; transitional cell carcinoma; transitional cell carcinoma metastatic; transitional cell carcinoma recurrent; transitional cell carcinoma urethra; trichoblastic carcinoma; triple hit lymphoma; triple negative breast cancer; tubular breast carcinoma; tumor associated fever; tumor budding; tumor cavitation; tumor cell mobilization; tumor fistulization; tumor flare; tumor hyperprogression; tumor invasion; tumor local invasion; tumor lysis syndrome; tumor necrosis; undifferentiated carcinoma of colon; undifferentiated nasopharyngeal carcinoma; undifferentiated sarcoma; ureteric cancer; ureteric cancer local; ureteric cancer metastatic; ureteric cancer recurrent; ureteric cancer regional; urethral cancer; urethral cancer metastatic; urethral cancer recurrent; urinary tract carcinoma in situ; uterine cancer; uterine carcinoma in situ; uterine leiomyosarcoma; uveal melanoma; vaginal adenocarcinoma; vaginal cancer; vaginal cancer metastatic; vaginal cancer recurrent; vaginal cancer stage 0; vaginal cancer stage i; vaginal cancer stage ii; vaginal cancer stage iii; vaginal cancer stage iva; vaginal cancer stage ivb; vulval cancer; vulval cancer metastatic; vulval cancer recurrent; vulval cancer stage 0; vulval cancer stage i; vulval cancer stage ii; vulval cancer stage iii; vulval cancer stage iv; vulvar adenocarcinoma; and yolk sac tumor site unspecified

Nausea/Vomiting MQG

Nausea; procedural nausea; procedural vomiting; vomiting; and vomiting projectile

Sinus Node Arrest, Pause, Block, Dysfunction MQG
Sinoatrial block; sinus arrest; and sinus node dysfunction

Upper Respiratory Infection, Cold, Rhinitis, Upper Respiratory Tract Infection MQG
Acute sinusitis; adenoviral upper respiratory infection; bacterial rhinitis; chronic sinusitis; epiglottitis; fungal pharyngitis; fungal rhinitis; influenza like illness; laryngitis; laryngitis viral; laryngopharyngitis; maxillary sinusitis; nasopharyngitis; pertussis; pharyngitis; pharyngitis bacterial; pharyngitis mycoplasmal; pharyngitis streptococcal; pharyngotonsillitis; respiratory tract infection; respiratory tract infection bacterial; respiratory tract infection viral; rhinitis; rhinitis hypertrophic; rhinitis seasonal; rhinitis ulcerative; sinobronchitis; sinusitis; sinusitis bacterial; staphylococcal pharyngitis; tonsillitis; tonsillitis streptococcal; upper respiratory fungal infection; upper respiratory tract congestion; upper respiratory tract infection; upper respiratory tract infection bacterial; viral pharyngitis; viral rhinitis; viral sinusitis; viral upper respiratory tract infection

Vomiting Fda B MQG
acetone vomiting; acute vestibular syndrome; cyclic vomiting syndrome; discolored vomit; epidemic vomiting syndrome; fecal vomiting; gastroenteritis viral; hematemesis; hyperemesis gravidarum; infantile spitting up; infantile vomiting; meniere's disease; meniere's disease aggravated; nausea; nausea aggravated; nausea post chemotherapy; nausea postoperative; obstruction gastric; post procedural nausea; post procedural vomiting; post-tussive vomiting; procedural nausea; procedural vomiting; regurgitation; regurgitation of food; retching; self-induced vomiting; small intestinal obstruction; vomiting; vomiting aggravated; vomiting in pregnancy; vomiting neonatal; vomiting nos; vomiting of medication; vomiting postoperative; vomiting projectile; and vomiting psychogenic

13.5. Recording and Reporting of ARIA, and Dose Modification and Treatment Discontinuations Related to ARIA

Recording of ARIA Events

ARIA events were recorded as adverse events and as MRI findings. The submission includes two datasets containing ARIA events, one recorded as adverse events and one as MRI findings.

ARIA-E findings were required to be reported as adverse events by investigators, but this was not specified for ARIA-H events.⁷² Consistent with this, this reviewer noted a higher number of participants experiencing at least one ARIA-H event in the MRI dataset compared to the adverse event dataset (differences greater than 50 participants).

⁷² Noted in a response dated September 2, 2022, to an information request dated September 1, 2022.

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The sponsor considered the MRI data to be the more comprehensive and definitive source for identification of ARIA-H rather than the adverse event dataset.⁷³

Small differences in the number of participants experiencing at least one ARIA-E event were noted in the adverse event and MRI datasets (difference < 5 participants). The sponsor noted that these differences were due in part to differences in timing of data entry in the two datasets relative to the data cutoff points.⁷⁴

Reviewer comment: This reviewer considered the dataset containing MRI findings to be the more comprehensive dataset for ARIA findings and as a result, analyses in this section used the MRI dataset unless otherwise specified.

Denominators for analyses in this section are the safety population (those who received at least one dose of study drug).

Reporting of ARIA in the Adverse Events Dataset

The sponsor notes that the protocols did not specify terminology for investigators to use if ARIA-H occurred; therefore, events of ARIA-H were recorded under multiple preferred terms.⁷⁵

For analyses of adverse events related to ARIA-H, the following preferred terms were used:

- Amyloid-related imaging abnormality-microhemorrhage and hemosiderin deposits
- Brain stem microhemorrhage
- Cerebellar microhemorrhage
- Cerebral hemosiderin deposit
- Cerebral microhemorrhage
- Superficial siderosis of the central nervous system

Reviewer comment: The sponsor proposed to include intracerebral hemorrhage as one of the terms contributing to ARIA-H; however, similar to events reported in the prescribing information for aducanumab and lecanemab, events related to intracerebral hemorrhage were evaluated separately from ARIA-H.⁷⁶

⁷³ Noted in a response dated July 1, 2022, to an information request dated June 29, 2022.

⁷⁴ Noted in a response dated September 15, 2022, to an information request dated September 13, 2022.

⁷⁵ Noted in a response dated September 2, 2022, to an information request dated September 1, 2022.

⁷⁶ Aduhelm. Labeling-Prescribing Information. Drugs@fda.gov. Action date April 29, 2022. Accessed September 6, 2022.

Although brain stem microhemorrhage is likely related to hypertension rather than amyloid, ARIA-E has been observed in the brainstem, and therefore, brainstem microhemorrhage remained in the group of ARIA-H.^{77,78}

For analyses related to ARIA-E using the adverse event dataset, the following preferred terms were used:

- Amyloid-related imaging abnormality edema/effusion
- Brain edema
- Vasogenic cerebral edema

In the event of finding ARIA-E on MRI, the investigator was to complete the case report form regarding the presence or absence of symptoms related to the ARIA-E.

Symptoms related to symptomatic ARIA-E events were captured in a dedicated case report form; however, seriousness of the symptoms was not collected.⁷⁹ If the event met ICH criteria for an SAE, the event was reported as an SAE. Studies AACG, AACH, and AACI did not have dedicated case report forms to collect ARIA-H symptoms.⁸⁰ Symptomatic ARIA-H was a notable event when serious or listed as a reason for discontinuation.

Similar to other AEs, ARIA events reported as adverse events were categorized as mild, moderate, and severe by the investigator based on severity assessment guidelines.

Recording and Reporting of ARIA in the MRI Dataset

In Study AACG, per study protocol, MRIs were performed at screening (within 9 weeks of Study Day 1), Weeks 4 (Visit 3, prior to the 2nd infusion), 12 (Visit 5, prior to the 4th infusion), 16 (Visit 6, prior to the 5th infusion), 24 (Visit 8, prior to the 7th infusion), 36 (Visit 11, prior to the 10th infusion), 52 (Visit 15, prior to the 14th infusion), 76, and the Early Discontinuation visit.

Additionally, the protocol indicated that an unscheduled MRI be performed if a participant developed more than one symptom suggestive of ARIA-E or a single symptom suggestive of ARIA-E of sufficient severity. If ARIA was present, then repeat MRIs every 4 to 6 weeks until resolution of ARIA-E or stabilization of ARIA-H was recommended. MRIs were read locally, and then sent to a centralized MRI vendor for analysis. The MRI at Week 12 (Visit 5) was to be performed and reviewed 2 weeks prior to the 4th donanemab infusion (Visit 5).

⁷⁷ Sperling R, Jack C, Black S, et al. Amyloid related imaging abnormalities (ARIA) in amyloid modifying therapeutic trials: recommendations from the Alzheimer's Association Research Roundtable Workgroup. *Alzheimers Dement*. 2011; 7(4): 367 – 385.

⁷⁸ Cogswell P, Barakos J, Barkhof F, et al. Amyloid-related imaging abnormalities with emerging Alzheimer's disease therapeutics: detection and reporting recommendations for clinical practice. *Am J Neuroradiol* 2022; 43: E19-E35.

⁷⁹ Noted in the sponsor's response dated October 13, 2022, to an information request dated October 4, 2022.

⁸⁰ Noted on page 32 of the Safety Update Report, submitted August 17, 2022.

In Study AACH Part B, MRIs were measured at an unscheduled visit if the participant's last MRI from Study AACG was greater than 12 months from Visit 1 of Part B, and at Week 4 (Visit 2, 2nd infusion), 12 (Visit 4, 4th infusion), 36 (Visit 10, 10th infusion), 72, and the Early Discontinuation visit. The MRI at Week 4 (Visit 2) was to be performed and reviewed prior to the 2nd donanemab infusion (Visit 2) and could occur no sooner than 21 days after the first infusion. The MRI performed at Visit 4 was to be performed and reviewed prior to the fourth infusion (given at Visit 4). The MRI at Visit 4 could occur 14 days before the scheduled visit date. If an infusion was suspended after the first, second, or third dose, an MRI was to be performed and reviewed prior to the fourth infusion.

In Study AACI Safety Addendum, MRIs were measured at Screening (within 49 days of Study Day 1), Weeks 4 (Visit 3, visit of the 2nd infusion), 12 (Visit 5, visit of the 4th infusion), 24 (Visit 8, visit of the 7th infusion), 52, 76, 82, 90, 102, 130, 154, and the Early Discontinuation visit. The MRI at Week 4 (Visit 3) was to be performed and reviewed prior to the 2nd donanemab infusion (Visit 3) and could occur no sooner than 21 days after the first infusion. The MRI performed at Visit 4 was to be performed and reviewed prior to the fourth infusion (given at Visit 4). The MRI at Visit 5 could occur 14 days before the scheduled visit date for Visit 5. If an infusion was suspended after the first, second, or third dose, an MRI was to be performed and reviewed prior to the fourth infusion.

In Study AACN Dona Cohort, MRIs were collected at screening (within 49 days of Study Day 1), Weeks 4 (Visit 3, visit of the 2nd infusion), 12 (Visit 5, visit of the 4th infusion), 24 (Visit 8, visit of the 7th infusion), and 44 (Visit 13, week of the 12th infusion). The MRI at Week 4 (Visit 3) was to be performed and reviewed prior to the 2nd donanemab infusion (Visit 3) and could occur no sooner than 21 days after the first infusion. The MRI at Week 12 (Visit 5) was to be performed and reviewed prior to the fourth donanemab infusion (Visit 5). The MRI at Visit 5 could occur 14 days before the scheduled visit date for Visit 5. The MRI at Week 24 (Visit 8) was to be performed and reviewed prior to the seventh donanemab infusion (Visit 8). The MRI at Visit 8 could occur 14 days before the scheduled visit date for Visit 8. The MRI at Week 44 (Visit 13) was to be performed and reviewed prior to the 12th donanemab infusion (Visit 13). The MRI at Visit 13 could occur 14 days before the scheduled visit date for Visit 13.

The following table shows when MRIs were scheduled by protocol relative to study infusion number in the Phase 2 and 3 studies.

Table 83. Schedule of MRIs Per Protocol Relative to Donanemab Infusion Number in Phase 2 and 3 Studies.

Study	MRI Obtained Prior to Infusion Number						
	2	4	5	7	10	12	14

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AACG	X	X	X	X	X		X
AACH Part B	X	X			X		
AACI Safety Addendum	X	X		X			
AACN	X	X		X		X	

ARIA-E and ARIA-H events were considered concurrent if they occurred on the same MRI scan.

ARIA-E was graded by a clinical research organization using a 3-point scale in Study AACG and a 5-point scale in Studies AACH, AACI, and AACN. The 3-point scale was used for integration of studies. The following table shows the ARIA-E MRI classification criteria used in the studies.

Table 84. ARIA-E MRI Classification Criteria

ARIA-E extent	ARIA-E focality	3-point scale	5-point scale
No ARIA-E	NA	0	0
< 5 cm	Monofocal	Mild (1)	Mild (1)
	Multifocal	Moderate (2)	Mild + (2)
5 – 10 cm	Monofocal		Moderate (3)
	Multifocal		Moderate + (4)
> 10 cm	Monofocal	Severe (3)	Severe (5)
	Multifocal		

The above table was submitted by the sponsor in an information response dated July 18, 2022, to an information request dated July 15, 2022.

The following figure shows ARIA-E severity rating scale in Study AACG.

Table 85. ARIA-E Severity Rating Scale for Study AACG

ARIA-E Severity Rating Scale

No/Questionable ARIA-E: *Normal to subtle sulcal or cortical FLAIR hyperintensity, most likely artifactual.*

Mild ARIA-E: *Mild FLAIR hyperintensity confined to sulcus and/or cortex/subcortex white matter (with or without gyral swelling and sulcal effacement), which affects an area of less than 5 cm in a single greatest dimension. Only a single region of involvement detected.*

Moderate ARIA-E: *Moderate involvement (area of FLAIR hyperintensity measuring 5-10 cm in single greatest dimension), or more than one site of involvement, each measuring less than 10 cm in a single greatest dimension.*

Severe ARIA-E: *Severe involvement (area of FLAIR hyperintensity measuring greater than 10 cm in single greatest dimension white matter) and /or sulcal involvement (with associated gyral swelling and sulcal effacement). One or more separate/independent sites of involvement may be noted.*

Non-evaluable: *Select when image quality is not sufficient to determine the presence or absence of ARIA-E (incorrect MRI parameters, motion degradation, missing FLAIR, etc.). Please provide reasons for why the images are not evaluable in the comments of Section 5.*

The figure was copied from the Brain MRI Worksheet Completion Guidelines noted in the sponsor's response dated September 2, 2022, to an information request dated September 1, 2022.

Similar ARIA-E severity rating scales were used for Study AACH, AACI, and AACN, except that moderate ARIA-E was further subdivided into the categories of mild+, moderate, and moderate+. ⁸¹

Mild, moderate, and severe categories were not used to grade ARIA-H radiographically. ⁸² Instead, ARIA-H radiographic findings were recorded based on shifts from baseline, and the following categories were used:

- no change from baseline
- microhemorrhage increase from baseline ≤ 4
- microhemorrhage increase from baseline >4
- microhemorrhage increase nonevaluable
- treatment-emergent superficial siderosis
- treatment-emergent macrohemorrhage (intracerebral hemorrhage)

⁸¹ Noted in Appendices 1, 2, and 3, in a response dated October 13, 2022, to an information request dated October 4, 2022.

⁸² Noted in a response dated September 2, 2022, to an information request dated September 1, 2022.

Microhemorrhages were defined as hemosiderin deposits ≤ 1 centimeter in diameter on the T2 sequence of an MRI in Study AACG.⁸³

In a response dated October 13, 2022, an information request by the Agency dated October 4, 2022, the sponsor reclassified ARIA-H according to the following table.

Table 86. ARIA MRI Classification Criteria

ARIA type	Radiographic Severity		
	Mild	Moderate	Severe
ARIA-H microhemorrhage	≤ 4 new incident microhemorrhages	5-9 new incident microhemorrhages	10 or more new incident microhemorrhages
ARIA-H superficial siderosis	1 new incident focal area of superficial siderosis	2 new incident focal areas of superficial siderosis	>2 new incident focal areas of superficial siderosis

Dose Modification for ARIA

The protocol for Study AACG included dose modifications for occurrence of ARIA-E. The following table shows dose modifications for the first occurrence of ARIA-E as noted in the protocol for Study AACG.

⁸³ Noted in the Brain MRI Worksheet Completion Guidelines for Study AACG on page 8 of the sponsor's response dated September 2, 2022, to an information request dated September 1, 2022.

Figure 2. Donanemab Dosage Modifications for First Occurrence of ARIA-E in Study AACG

ARIA-E SYMPTOMS	ARIA-E on MRI		
	Mild	Moderate	Severe
No symptoms	Continue on current dosing ^a	LY3002813 Dose reduction ^{a,b}	Temporary Discontinuation of LY3002813 (refer to Section 8.1.1.1) ^b
Mild	LY3002813 Dose reduction ^{a,b}	Temporary Discontinuation of LY3002813 (refer to Section 8.1.1.1) ^b	Temporary Discontinuation of LY3002813 (refer to Section 8.1.1.1) ^b
Moderate	Temporary Discontinuation of LY3002813 (refer to Section 8.1.1.1) ^b	Temporary Discontinuation of LY3002813 (refer to Section 8.1.1.1) ^b	Temporary Discontinuation of LY3002813 (refer to Section 8.1.1.1) ^b
Severe	Temporary Discontinuation of LY3002813 (refer to Section 8.1.1.1) ^b	Temporary Discontinuation of LY3002813 (refer to Section 8.1.1.1) ^b	Temporary Discontinuation of LY3002813 (refer to Section 8.1.1.1) ^b

^a Investigator may choose to temporarily discontinue LY3002813 after discussion with the sponsor.

^b If the patient has a second incidence of ARIA-E and has previously been dose reduced or temporarily discontinued from LY3002813, then LY3002813 will be permanently discontinued (see Section 8.1).

Noted on page 52 of AACG 05 protocol – d submitted by the applicant.

If dose reduction was required, the donanemab dose was reduced to the next lower dose (700 mg for a 1400 mg dose or placebo for a 700 mg dose). All cases of ARIA-E required further unscheduled MRI scans every 4-6 weeks until ARIA-E has resolved. If the study drug was restarted, patients were given donanemab 700 mg or placebo, depending on the original study arm to which the patient was randomized. An unscheduled safety MRI was required 4-6 weeks after dose restarts. If ARIA-E symptoms and radiologic findings were not completely resolved within 16 weeks, the patient was permanently discontinued from donanemab treatment.

In Study AACG, no dose reductions were done for ARIA-H. Patient were discontinued from dosing if they developed any increase in ARIA-H accompanied by clinically significant symptoms; had >4 new microhemorrhages, > 1 new area of superficial siderosis or significant worsening of pre-existing superficial siderosis; or any intracerebral hemorrhage, regardless of symptoms. All new cases of ARIA-H required unscheduled MRI scans every 4-6 weeks until ARIA-H has stabilized without new findings.

In contrast to Study AACG, Studies AACH Part B, AACI Safety Addendum, and AACN-Dona cohort did not include dose reduction for the development of ARIA. In these three studies, for participants who developed ARIA during the titration period, the study drug could be temporarily suspended, continue at 700 mg dose temporarily or throughout the remainder of the treatment period, or increased to 1400 mg dose if the participant had received three doses of 700 mg.

Studies AACH Part B, AACI Safety Addendum, and AACN-Dona Cohort had more permissive dosing in ARIA-H management compared to Study AACG. The following figure shows guidance for management of ARIA-H in Study AACH Part B from the Manual of Operations.

Table 87. Guidance for Management of ARIA-H in the Manual of Operations for Study AACH Part B

ARIA-H Microhemorrhage (MCH), Superficial Siderosis	Asymptomatic	≤ 10 new MCH from baseline and/or ≤ 2 Superficial Sideroses	- Hold IP if > 4 new MCH or ≥ 1 new Superficial Siderosis within first 3 doses otherwise may continue IP - Monitor with unscheduled MRIs monthly
		> 10 new MCH from baseline and/or > 2 Superficial Sideroses	- Hold IP - Monitor with unscheduled MRIs monthly - Upon stabilization of MCH on imaging, consider re-initiating IP (stabilization defined as no new MCH and no increase in extent of MCH on subsequent MRI)
	Symptomatic	Any Severity	- Hold IP - Monitor with unscheduled MRIs monthly - If resolution of symptoms is not observed, permanently discontinue IP, but continue other study activities - If ARIA-H symptoms are clearly related to an SAE, then permanently discontinue IP, but continue other study activities

Noted on pages 88 of the response dated July 18, 2022, to an information request dated July 15, 2022.

The following figure shows guidance for management of ARIA-E in Study AACH Part B.

Table 88. Guidance for Management of ARIA-E in the Manual of Operations for Study AACH Part B

Finding	Symptoms	MRI Severity	Guidance
ARIA-E	Asymptomatic	1 Mild 2 Mild +	Monitor with unscheduled MRIs monthly until resolution
		3 Moderate	- Hold IP if severity 3 and occurs within first 3 doses otherwise may continue IP - Monitor with unscheduled MRIs monthly until resolution
		4 Moderate + 5 Severe	- Hold IP - Monitor with unscheduled MRIs monthly - Upon resolution of ARIA-E on imaging, consider re-initiating IP - If resolution is not observed, permanently discontinue IP, but continue other study activities
	Symptomatic	Any Severity	- Hold IP - Monitor with unscheduled MRIs monthly - Upon resolution of ARIA-E on imaging and resolution of clinical symptoms, consider re-initiating IP - If resolution of ARIA-E or resolution of symptoms are not observed, permanently discontinue IP, but continue other study activities - If ARIA-E symptoms are clearly related to an SAE, then permanently discontinue IP, but continue other study activities

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Noted on pages 88 of the response dated July 18, 2022 to an information request dated July 15, 2022.

Studies AACI and AACN had similar management of ARIA-E and ARIA-H. Study drug was permanently discontinued for cases of intracerebral hemorrhage in all three studies

Indications Related to ARIA Leading to Permanent Treatment Discontinuation by Protocol

Per Study AACG protocol, treatment with donanemab was permanently discontinued in patients for the following conditions related to ARIA:

- Second incidence of ARIA-E that occurred after a previous dose reduction or temporary discontinuation of donanemab
- Any increase in ARIA-H accompanied by clinically significant symptoms
- >4 new microhemorrhages, > 1 new area of superficial siderosis or significant worsening of pre-existing superficial siderosis, or any intracerebral hemorrhage, regardless of symptoms
- An ARIA-E event reported as an SAE

The protocols for Studies AACH Part B, AACI Safety Addendum and AACN Dona-Cohort differed from the protocol for Study AACG for indications leading to permanent discontinuation for ARIA-related conditions and included the following conditions:

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

13.6. AE Severity and Radiographic Severity in Participants with Symptomatic ARIA in Study AACG

The following table shows AE severity and radiographic severity in participants with symptomatic ARIA in Study AACG.

Table 89. AE Severity and Radiographic Severity in Participants with Symptomatic ARIA in Study AACG

USUBJID	Adverse Event	AE Start Date	AE End Date	SER	AE Severity	Date of MRI and Radiographic Severity
I5T-MC-AACG- (b) (6)	V: ARIA-E	(b) (6)	(b) (6)	N	MOD	AE onset: MOD
(b) (6)	D: ARIA-E					

USUBJID	Adverse Event	AE Start Date	AE End Date	SER	AE Severity	Date of MRI and Radiographic Severity
C: e4e4 T: PBO	V: Fall with no injury	(b) (6)	(b) (6)	N	MOD	(b) (6) NP (b) (6) : (b) (6) MOD
	D: Fall					
	V: Intermittent Dizziness	(b) (6)	(b) (6)	N	MOD	(b) (6) NP (b) (6) : (b) (6) MOD
	D: Dizziness					
I5T-MC-AACG- (b) (6) (b) (6) 1 C: e3e4 T: DON	V: Intermittent Vertigo	(b) (6)	(b) (6)	N	MOD	(b) (6) NP (b) (6) : (b) (6) MOD
	D: Vertigo					
	CIOMS form: Confusion, expressive aphasia	(b) (6)	Not recorded	Not recorded	Not recorded	(b) (6) NP (b) (6) : (b) (6) SEV
I5T-MC-AACG- (b) (6) (b) (6) 2 C: e3e4 T: DON	V: Headache	(b) (6)	(b) (6)	N	MILD	(b) (6) MILD (b) (6) : (b) (6) MOD
	D: Headache					
	V: Subtle worsening of cognitive function (word finding and spelling)	(b) (6)	ongoing	N	MILD	(b) (6) MILD (b) (6) : (b) (6) MOD
	D: cognitive disorder					
I5T-MC-AACG- (b) (6) (b) (6) C: e4e4 T: DON	V: ARIA-E	(b) (6)	(b) (6)	Y	SEV	(b) (6) NP (b) (6) : (b) (6) SEV
	D: ARIA-E					

USUBJID	Adverse Event	AE Start Date	AE End Date	SER	AE Severity	Date of MRI and Radiographic Severity
I5T-MC-AACG- (b) (6) (b) (6) 2 C: no e4 T: DON	V: Headache D: Headache	(b) (6)	(b) (6)	N	MILD	(b) (6) NP (b) (6) SEV
	V: Nausea D: Nausea	(b) (6)	(b) (6)	N	MILD	(b) (6) NP (b) (6) SEV
	V: Vomiting D: Vomiting	(b) (6)	(b) (6)	N	MILD	(b) (6) NP (b) (6) SEV
	V: Fatigue D: Fatigue	(b) (6)	Not recovered	N	MOD	(b) (6) NP (b) (6) SEV
I5T-MC-AACG- (b) (6) (b) (6) C: no e4 T: DON	V: Worsening of headache D: Headache	(b) (6)	X	N	MOD	(b) (6) NP (b) (6) SEV

C: ApoE e4 carrier status, D: Dictionary derived term, DON: donanemab, MOD: moderate, NP: Not present, PBO: placebo, SER: Seriousness, T: Treatment, V: Verbatim Term

¹Per the sponsor's response dated January 9, 2023, to an information request dated January 9, 2023, symptoms noted on the CIOMS were not recorded as AEs.

²Verbatim terms and dictionary derived terms noted in the sponsor's response dated January 9, 2023, to an information request dated January 9, 2023.

13.7. Frequency of ARIA by ApoE ε4 Carrier Status, Concomitant Antithrombotic Medication use, Sex, Age Group, and Presence of Microhemorrhage at Baseline in the All-Donanemab Pool

In participants in the all-donanemab pool, serious ARIA-E occurred at higher frequency in homozygous carriers for ApoE ε4 compared to noncarriers (3% versus 0%, respectively). Radiographically severe ARIA was observed at higher frequencies in homozygote carriers compared to noncarriers in (ARIA-E: 3% versus 1%, ARIA-H: 14% versus 2%, respectively). The

following table shows serious ARIA events and ARIA events by radiographic severity and ApoE ε4 carrier status in the all-donanemab pool at the 90-Day Safety Update.

Table 90. Serious ARIA and Radiographic Severity of ARIA by ApoE ε4 Carrier Status in the All-Donanemab Pool at the 90-Day Safety Update.

Category	Donanemab N=1304		
	NC N=463 n (%)	HET N=669 n (%)	HOM N=160 n (%)
ARIA-E	43 (9)	128 (19)	55 (34)
Serious ARIA-E	1 (<0.5)	2 (<0.5)	4 (3)
Mild	19 (4)	57 (9)	12 (8)
Moderate	18 (4)	62 (9)	38 (24)
Severe	5 (1)	9 (1)	5 (3)
ARIA-H	62 (13)	127 (19)	60 (38)
Serious ARIA-H	0	0	4 (3)
Mild	48 (10)	87 (13)	27 (17)
Moderate	7 (2)	20 (3)	11 (7)
Severe	7 (2)	20 (3)	22 (14)

HET: heterozygous status, HOM: homozygous status, NC: noncarrier status. Mild, moderate, and severe categories are based on maximum radiographic severity.

Donanemab-treated participants with concurrent antithrombotic use did not have a higher frequency of ARIA compared to participants without concurrent antithrombotic use in the all-donanemab pool. A similar frequency of intracerebral hemorrhage > 1 cm was observed between participants with and without concurrent antithrombotic use (0.2% versus 0.1%, respectively). The following table shows the frequency of ARIA and intracerebral hemorrhage > 1 cm based on concomitant antithrombotic use within 30 days prior to onset of the event in the all-donanemab pool at the 90-Day Safety Update.

Table 91. Frequency of ARIA and Intracerebral hemorrhage > 1 cm based on Concomitant Antithrombotic Medication Use in the All-Donanemab Pool at the 90-Day Safety Update¹.

Event	Antithrombotic Use	Donanemab N=1304
ARIA	Yes	121 (9.3)
	No	199 (15.3)
ARIA-E	Yes	84 (6.4)
	No	145 (11.1)
ARIA-H	Yes	99 (7.6)

Event	Antithrombotic Use	Donanemab N=1304
	No	153 (11.7)
ARIA-H Microhemorrhage	Yes	79 (6.1)
	No	124 (9.5)
ARIA-H Superficial siderosis	Yes	44 (3.4)
	No	61 (4.7)
Intracerebral hemorrhage > 1 cm	Yes	2 (0.2)
	No	1 (0.1)

¹Antithrombotic use considered concomitant when occurring within 30 days prior to onset of event. Data from this table is taken from the sponsor's response dated October 13, 2022, to an information request dated October 4, 2022 and a response dated November 3, 2022, to an information request dated November 2, 2022

Acetylsalicylic acid was the most frequently occurring antithrombotic used in the pooled studies. The following table shows the frequency of subjects with use of antithrombotic medications at any point or within 57 days of the end of the study in the all-donanemab pool at the 90-Day Safety Update.

Table 92. Frequency of Subjects with Antithrombotic Medication Use in the All-Donanemab Pool at the 90-Day Safety Update.

Category	DON N=1304 n (%)
Antithrombotic	545 (42)
Acetylsalicylic acid-containing products	417 (32)
Non-acetylsalicylic acid antiplatelets	59 (5)
Anticoagulants	153 (12)

Medications were used at any time within the studies or within 57 days of the end of the study. The reviewer created this table using the ADCM submitted on August 25, 2022, ADSL.LYMTRTFL=Y, LYIN57FL=Y, ANTITHFL=Y, grouped on USUBJID.

In the all-donanemab pool, ARIA-E, ARIA-H and intracerebral hemorrhage > 1 cm occurred with similar frequency between females and males (difference ≤ 3%). The following table shows frequency of ARIA and intracerebral hemorrhage > 1 cm based on sex in the all-donanemab pool at the 90-Day Safety Update.

Table 93. Frequency of ARIA and Intracerebral Hemorrhage > 1 cm Based on Sex in the All-Donanemab Pool at the 90-Day Safety Update.

Event	DON N=1304	
	Female N=699 n (%)	Male N=605 n (%)
ARIA	180 (26)	140 (23)
ARIA-E	132 (19)	97 (16)
ARIA-H	126 (18)	126 (21)
ARIA-H Microhemorrhage	103 (15)	100 (17)
ARIA-H Superficial siderosis	51 (7)	54 (9)
Intracerebral hemorrhage > 1 cm	2 (<0.5)	1 (<0.5)

The reviewer created this table using the IDB ADXP submitted on October 13, 2022, LYMTRTFL = Y, TELY57FL = Y, PARAM = Severity of ARIA-E, ARIA-H, ARIA-H MH, and ARIA-H SS, then grouped on USUBJID, PARAM, SEX.

ARIA-E occurred with higher frequency in participants < 75 years of age compared to ≥75 years of age in the all-donanemab pool (22% versus 14%, respectively). The following table shows the frequency of ARIA and intracerebral hemorrhage > 1 cm based on age group < 75 and ≥75 years of age in the all-donanemab pool at the 90-Day Safety Update.

Table 94. Frequency of ARIA and Intracerebral Hemorrhage > 1 cm Based on Age Group in the All-Donanemab Pool at the 90-Day Safety Update.

Event	DON N=1304	
	< 75 years N=589 n (%)	≥75 years N=715 n (%)
ARIA	151 (26)	169 (24)
ARIA-E	127 (22)	102 (14)
ARIA-H	106 (18)	115 (16)
ARIA-H Microhemorrhage	85 (14)	118 (17)
ARIA-H Superficial siderosis	48 (8)	57 (8)
Intracerebral hemorrhage > 1 cm	0	3(<0.5)

The reviewer created this table using the IDB ADXP submitted on October 13, 2022, LYMTRTFL = Y, TELY57FL = Y, PARAM = Severity of ARIA-E, ARIA-H, ARIA-H MH, and ARIA-H SS, then grouped on USUBJID, PARAM, AGEGR2.

Higher frequencies of ARIA-E, ARIA-H microhemorrhage and ARIA-H superficial siderosis were observed in participants with microhemorrhage present at baseline compared to participants without microhemorrhage present at baseline in the all-donanemab pool. The following table shows the frequency of ARIA and intracerebral hemorrhage > 1 cm based on presence of microhemorrhage on baseline MRI in the all-donanemab pool.

Table 95. Frequency of ARIA and Intracerebral Hemorrhage > 1 cm Based on Presence of Microhemorrhage at Baseline in the All-Donanemab Pool at the 90-Day Safety Update.

Event	DON N=1304	
	BMH Not Present N=1128 n (%)	BMH Present N=176 n (%)
ARIA	247 (22)	73 (41)
ARIA-E	178 (16)	51 (29)
ARIA-H	186 (16)	66 (38)
ARIA-H Microhemorrhage	152 (13)	51 (29)
ARIA-H Superficial siderosis	69 (6)	36 (20)
Intracerebral hemorrhage > 1 cm	3 (<0.5)	0

BMH: baseline microhemorrhage. The reviewer created this table using the IDB ADXP submitted on October 13, 2022, LYMTRTL = Y, PARAM = number of microhemorrhages present, ABLFL=Y, where Yes = AVAL = 1 through 4 and No = AVAL = 0, joined with IDB ADXP submitted on October 13, 2022, LYMTRTL = Y, TELY57FL=Y, PARAM = severity of ARIA-E and ARIA-H, grouped on USUBJID, AVAL.

13.8. TEAEs Belonging to the SMQs of Anaphylactic Reaction, Hypersensitivity, and Angioedema (Narrow) by Severity in the All-Donanemab Pool at the 90-Day Safety Update

Table 96. TEAEs Belonging to the SMQs of Anaphylactic Reaction, Hypersensitivity, and Angioedema (Narrow) by Severity in the All-Donanemab Pool at the 90-Day Safety Update

TEAE Severity	DON N=1304 n (%)
Participant Reporting at Least One TEAE	151/151 (100)
Mild	104/151 (69)
Moderate	49/151 (32)
Severe	10/151 (7)

The reviewer created this using the IDB ADAE dataset submitted 8.25.22, TRT01A = inversion of Dona-C, SAFFL = Yes, LYIN57FL = Yes, TRTEMFL = Yes, select row where SMQ12SC, 13SC, or 14SC = NARROW, grouped on USUBJID, AESEV.

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13.9. References

13.10. Financial Disclosure

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

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