DONANEMAB FOR THE TREATMENT OF PATIENTS WITH EARLY SYMPTOMATIC ALZHEIMER'S DISEASE

SPONSOR BRIEFING DOCUMENT

PERIPHERAL AND CENTRAL NERVOUS SYSTEM DRUGS ADVISORY COMMITTEE

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List of Abbreviations

Term	Definition
AChEI	acetylcholinesterase inhibitor
AD	Alzheimer's disease
ADA	antidrug antibody
ADAS-Cog$_{13}$	Alzheimer's Disease Assessment Scale – 13-item Cognitive Subscale
ADCS-iADL	Alzheimer's Disease Cooperative Study – instrumental Activities of Daily Living subscale
ADR	adverse drug reaction
AE	adverse event
All Dona	donanemab-treated integrated safety analysis population
APOE	gene coding for apolipoprotein class E
APOE ε4	allele subtype 4 of the gene coding for apolipoprotein class E
ARIA	amyloid-related imaging abnormalities
ARIA-E	amyloid-related imaging abnormalities–edema/effusions (also known as vasogenic edema)
ARIA-H	amyloid-related imaging abnormalities–hemorrhage/hemosiderin deposition (including brain microhemorrhage and superficial siderosis)
AUC$_{(0-\infty)}$	area under the concentration versus time curve from zero to infinity
AUC$_{\tau}$	area under the concentration versus time curve during one dosing interval
AUC$_{\tau,ss}$	area under the concentration versus time curve during one dosing interval at steady state
CDR-G	Clinical Dementia Rating Scale – Global score
CDR-SB	Clinical Dementia Rating Scale – Sum of Boxes
CI	confidence interval
CL	Centiloid
C_{max}	maximum observed concentration
$C_{max,ss}$	maximum observed concentration at steady state
COVID-19	coronavirus disease 2019

Term	Definition
C-SSRS	Columbia-Suicide Severity Rating Scale
CT	computed tomography
$C_{trough,ss}$	predose concentration observed at steady state
CYP450	cytochrome P450
Dona-PC	placebo-controlled safety analysis population
GFAP	glial fibrillary acidic protein
High tau population, Study AACI	efficacy analysis population that only includes patients with high tau pathology
HR	hazard ratio
iADRS	integrated Alzheimer's Disease Rating Scale
IRR	infusion-related reaction
IV	intravenous
Low-medium tau population, Study AACI	efficacy analysis population that only includes patients with low to medium (intermediate) tau pathology
LTE	long-term extension
mAb	monoclonal antibody
Macrohemorrhage	intracerebral hemorrhage greater than 1 cm
MCI	mild cognitive impairment
MMRM	Mixed Model for Repeated Measures
MMSE	Mini-Mental State Examination
MRI	magnetic resonance imaging
MWPC	meaningful within-patient change
NCS	natural cubic spline
Overall population, Study AACI	efficacy analysis population that includes patients with low-medium and high tau pathology
PD	pharmacodynamic(s)
PET	positron emission tomography
PK	pharmacokinetic(s)

Term	Definition
P-tau217	tau phosphorylated at threonine 217, also called phospho-tau 217
Q4W	every 4 weeks
SAE	serious adverse event
SD	study day
SE	standard error
Study AACG	Study I5T-MC-AACG, also called TRAILBLAZER-ALZ
Study AACH	Study I5T-MC-AACH, also called TRAILBLAZER-EXT
Study AACI	Study I5T-MC-AACI, also called TRAILBLAZER-ALZ2
Study AACI-LTE	Study I5T-MC-AACI, Long-Term Extension study period
Study AACN	Study I5T-MC-AACN, also called TRAILBLAZER-ALZ4
SUVr	standardized uptake value ratio
TEAE	treatment-emergent adverse event

1. EXECUTIVE SUMMARY

1.1. Introduction

Eli Lilly and Company (Lilly) is seeking approval of donanemab for the treatment of patients with Alzheimer's disease (AD) presenting with mild cognitive impairment or mild dementia and with confirmed amyloid pathology.

The efficacy and safety of donanemab for this proposed indication were investigated in a registration-quality Phase 2 study (TRAILBLAZER-ALZ, AACG) and a Phase 3 study (TRAILBLAZER-ALZ2, AACI). The studies demonstrated substantial evidence of efficacy and clinically meaningful slowing of disease progression. The efficacy results were consistent across trials, populations, and endpoints, with greater relative benefit for those treated earlier in their course of disease. The program also advances the scientific understanding of amyloid and tau in the clinical course of Alzheimer's disease and enabled limited duration dosing. The safety profile of donanemab has been well characterized. With appropriate labeling and management, the potential risks are outweighed by the demonstrated benefits on the clinical endpoints in patients with AD.

The FDA has called on the Peripheral and Central Nervous System Drug Advisory Committee to consider key review topics prior to taking action on the donanemab Biologics License Application. Lilly recognizes the societal importance of ensuring that this emerging class of amyloid-targeting disease-modifying therapies for AD are well characterized with favorable benefit-risk profiles. As such, we welcome the opportunity to share these data with the community and the Peripheral and Central Nervous System Drug Advisory Committee.

Based on our communications with the FDA regarding the decision to convene the advisory committee, the following topics are addressed in support of the expected discussion:

- prospective characterization of tau levels in patients enrolled to the donanemab development program
- the optimal approach to donanemab treatment duration
- the safety profile of donanemab, focusing on an assessment of mortality risk, and
- the overall benefit-risk of donanemab for the proposed indicated patient population.

1.2. Background and Unmet Need

AD is a progressive and ultimately fatal neurodegenerative condition. When compared with patients without dementia, the risk of mortality for patients with AD is increased 4-fold with an average life expectancy of 6 years after diagnosis (Liang et al. 2021). Incidence rates (IR) of death increase with increasing disease severity, that is, from 1.6 in patients without dementia to 4.3 in patients newly diagnosed with mild cognitive impairment, and to 10.6 per 100 patient-years in patients newly diagnosed with AD (Steenland et al. 2010). This fatal disease will affect an estimated 6.9 million Americans older than 65 years of age in 2024 (Alzheimer's Association 2024).

The clinical course of AD involves progressive memory loss, behavioral alteration, gait and motor disturbances, and declining ability to perform activities of daily living. Eventually, patients become completely dependent on a caregiver, which is usually followed by nursing home care (Bynum et al. 2004) and eventually death. No patient has ever recovered from AD. The progressive loss of independence of patients with AD results in a tremendous burden to caregivers, families, and to our society (Alzheimer's Association 2023).

Currently, the most frequently used treatment options only provide temporary relief of AD symptoms. These include acetylcholinesterase inhibitors and the N-methyl D-aspartate receptor antagonist (memantine). Both have been shown to provide symptomatic benefit in patients with AD, but do not impact the underlying cause of the disease or modify disease progression.

In the brain, the presence of amyloid is a key pathological hallmark, and is thought to be an initiating step in a cascade leading to accumulation and spread of abnormally aggregated tau protein (neurofibrillary tangles), neuronal dysfunction, cognitive impairment, and eventually neurodegeneration and death. Recent clinical studies have suggested that effective removal of amyloid plaque can slow the cognitive deterioration of AD. Two disease-modifying therapies have been approved by the FDA, lecanemab (Leqembi® [Eisai R&D Management Co., Ltd. Nutley, NJ]) and aducanumab (Aduhelm® [Biogen, Cambridge, MA]), but aducanumab is no longer actively marketed by the sponsor.

However, one available therapy is not sufficient. Patients, caregivers and providers deserve multiple disease-modifying options to treat this complex, progressive disease. This is especially important given the serious and ultimately fatal nature of AD, and the major public health burden for patients, caregivers, and society. Donanemab offers meaningful clinical benefit with a potential to stop treatment when treatment-related amyloid clearance is achieved, and provides an additional and clinically important disease-modifying treatment for Alzheimer's patients.

More information on the existing unmet need is summarized in Section 2.

1.3. Donanemab for the Treatment of AD

Donanemab has been developed under the hypothesis that targeting insoluble aggregated brain amyloid (amyloid plaques) will remove a key initiating event for AD thereby slowing clinical progression, particularly in the earlier stages of the disease.

Donanemab is a monoclonal antibody specific for an insoluble form of amyloid beta present only in brain amyloid plaques, known as N-truncated pyroglutamate amyloid beta (Bridel et al. 2017). Donanemab binds to the deposited amyloid plaque and aids its removal through microglial-mediated phagocytosis (DeMattos et al. 2012).

In Phase 1 development, donanemab showed a speed and depth of plaque clearance that exceeded other antibodies previously tested. Phase 1 studies also demonstrated the durability of plaque clearance after dosing cessation (Lowe et al. 2021a, 2021b). Based on these observations, donanemab was advanced into full development by Lilly. The robust amyloid-lowering properties of donanemab, combined with selectivity for insoluble plaque, provided the unique

opportunity to evaluate an individualized time-limited treatment approach in the registration development program.

More information on the product is summarized in Section 3.

1.4. Lilly's Development of Biomarkers for Use in Alzheimer's Disease Drug Development

Over the past 3 decades, AD development programs have evolved from enrolling patients solely based on clinical symptoms, to now enrolling patients based on the confirmed presence of amyloid pathology. This innovation in diagnostic testing (accelerated by the first FDA approval of an amyloid-imaging agent in 2012), also permitted a shift towards enrolling patients with less severe cognitive impairment where intervention was more likely to be beneficial. In 2013, the presence of amyloid pathology (confirmed by amyloid positron emission tomography [PET] imaging) was required by Lilly for the first time in large-scale Phase 3 AD study (EXPEDITION 3 study of solanezumab; Honig et al. 2018)—something other sponsors were only doing in small subsets of enrolled patients.

As our understanding of AD pathology increased over the ensuing decade, it became clear that brain tau (in addition to amyloid) levels were an important prognostic marker for disease progression. The first tau imaging agent was approved by the FDA in 2020. Given its prognostic importance, Lilly prospectively characterized all patients enrolled in a study for brain tau levels—whereas again, other sponsors had done this only in small subsets of enrolled patients. Specifically, patients enrolled in the donanemab Phase 2 and Phase 3 pivotal studies were prospectively characterized for both the presence and quantity of brain tau pathology. As outlined in detail below, this prospective characterization of tau was undertaken to:

- ensure treatment groups were well balanced for disease burden
- increase the likelihood that the study could clearly determine drug effect by enrolling patients who were likely to experience measurable clinical deterioration during the constraints of an 18-month study period
- further the field's scientific understanding of AD, and
- continue to innovate upon the clinical trial paradigm and thereby accelerate development of future therapies.

Of note, while patients were prospectively characterized for tau levels in the context of the highly controlled, and rigorously conducted donanemab development program for the reasons outlined above, tau levels were not designed to become a prospective patient selection factor in clinical practice for the following reasons:

- There is no mechanistic basis to believe that with an amyloid-targeted therapy, such as donanemab, there is a specific tau level at which this mechanism of action would not be potentially beneficial.
- The measurement of tau levels is not standardized and therefore could not be readily implemented in routine clinical practice. Moreover, access to tau imaging is not generally available even in clinical practice.

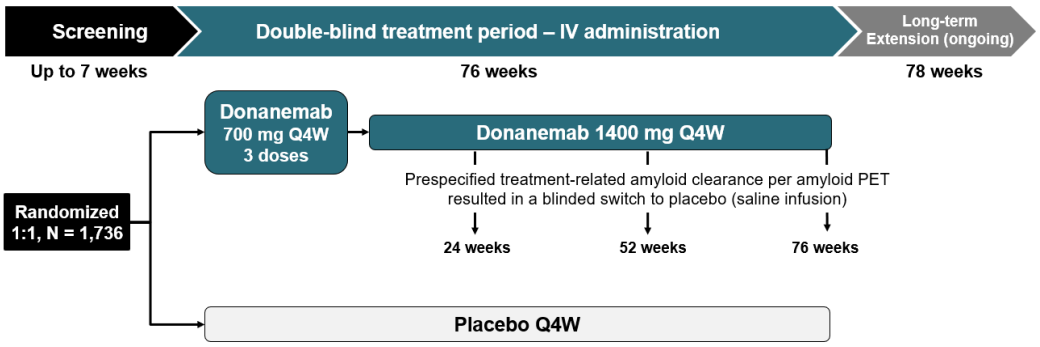
- In contrast to assessment of the presence of amyloid (which is required for drug effect), tau levels are prognostic of disease progression and not predictive of drug response.

More information on the development program is summarized in Section 4.1.

1.5. Donanemab Phase 3 Study Design and Enrolled Population

Study AACI was a multicenter, randomized, double-blind, placebo-controlled Phase 3 study that enrolled patients who had early symptomatic AD and were positive for brain amyloid by PET scan. Patients were randomly assigned in a 1:1 ratio to receive either donanemab or placebo. Patients were stratified according to tau levels (low-medium tau vs high tau). Patients in the donanemab group received 700 mg intravenous infusion every 4 weeks for 3 doses and then 1400 mg thereafter for up to 72 weeks. Patients administered the 1400 mg dose continued the 1400 mg dose until the end of the study unless they became eligible to discontinue donanemab treatment and move to placebo in a blinded manner, based on predefined amyloid clearance imaging criteria, following an amyloid PET scan at 24, 52, and 76 weeks.

More information on the clinical trial design is summarized in Section 6.2.1.



Abbreviations: AACI = I5T-MC-AACI; IV = intravenous; N = number of patients; PET = positron emission tomography; Q4W = every 4 weeks.

Figure 1.1. Study design of Study AACI.

Compared with other contemporary AD studies, the donanemab program enrolled an older and more clinically advanced population (by clinical scale/stage assessment, and larger portion with symptomatic AD medication use) with higher pathological disease burden (higher baseline amyloid plaque level) and larger portion of allele subtype 4 of the gene coding for apolipoprotein class E [APOE ε4] carriers and homozygotes. These baseline characteristic differences are expected to have resulted in a population that was both harder to treat, and more susceptible to both drug-related as well as unrelated adverse events (AEs) or death due to comorbid illness.

Demographic and baseline characteristics of the program are summarized in Section 6.2.

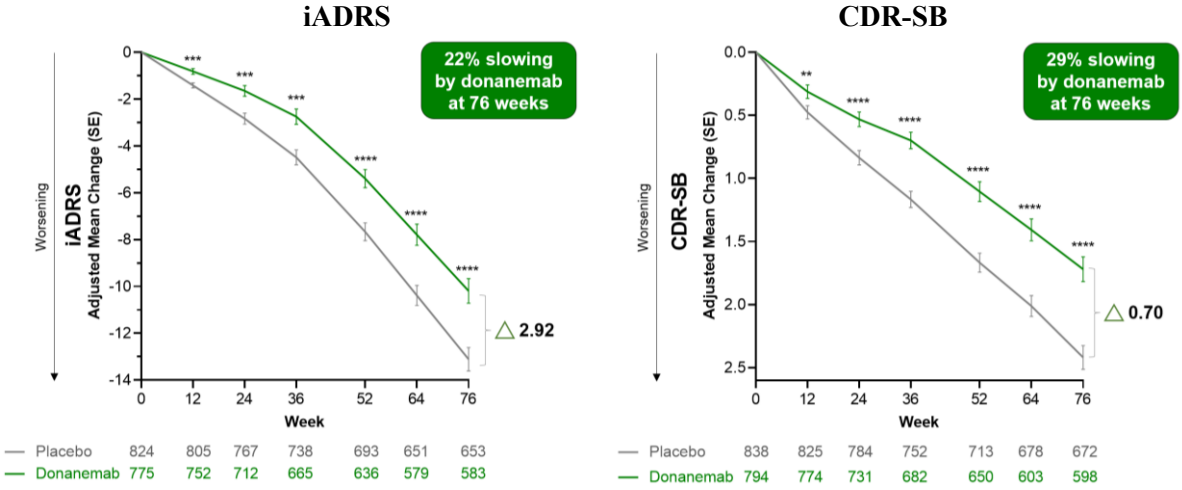
1.6. Efficacy Results

In Study AACI, donanemab demonstrated clinically meaningful benefit across all multiplicity controlled primary and secondary clinical endpoints assessing efficacy in both cognition and

function (Table 6.5). Importantly, the magnitude of impact on these clinical endpoints meets, and in several respects exceeds prior approvals for demonstration of clinical benefit and effectiveness in AD. Study AACI results also marked the first time, and only instance to date, where a disease-modifying drug for AD showed replication of prespecified results across 2 different positive studies; the registration-quality Phase 2 Study AACG and Phase 3 Study AACI both showed statistically significant and highly similar efficacy on the primary integrated Alzheimer's Disease Rating Scale (iADRS) endpoint. Results from the Phase 2 Study AACG are summarized in Section 6.1.

On the primary endpoint in Study AACI, patients treated with donanemab demonstrated a statistically significant and clinically meaningful reduction in clinical decline on iADRS, compared with placebo at Week 76 in the overall population (2.92, p<0.0001; Figure 1.2). The iADRS is a clinical efficacy measure that integrates assessment of cognition and daily function. It is a summation of scores on 2 widely used measures (Alzheimer's Disease Assessment Scale – 13-item Cognitive Subscale [ADAS-Cog$_{13}$] measuring cognition and Alzheimer's Disease Cooperative Study – instrumental Activities of Daily Living subscale [ADCS-iADL] measuring function). These 2 measures are accepted as coprimaries in AD studies, and in Study AACI each was statistically significant on its own with a similar treatment effect observed.

Patients treated with donanemab also demonstrated a statistically significant and clinically meaningful reduction in clinical decline on Clinical Dementia Rating Scale – Sum of Boxes (CDR-SB), across all domains of the scale, compared with placebo at Week 76 in the overall population (-0.70, p<0.0001; Figure 1.2). The CDR-SB, a global assessment tool that evaluates both cognition and function, is a more commonly used clinical study endpoint in early-stage AD studies and is used as the primary basis for regulatory review and labeling.



Abbreviations: AACI = I5T-MC-AACI; iADRS = integrated Alzheimer's Disease Rating Scale; CDR-SB = Clinical Dementia Rating Scale – Sum of Boxes; SE = standard error.
Note: ** p<0.01, *** p<0.001, **** p<0.0001.

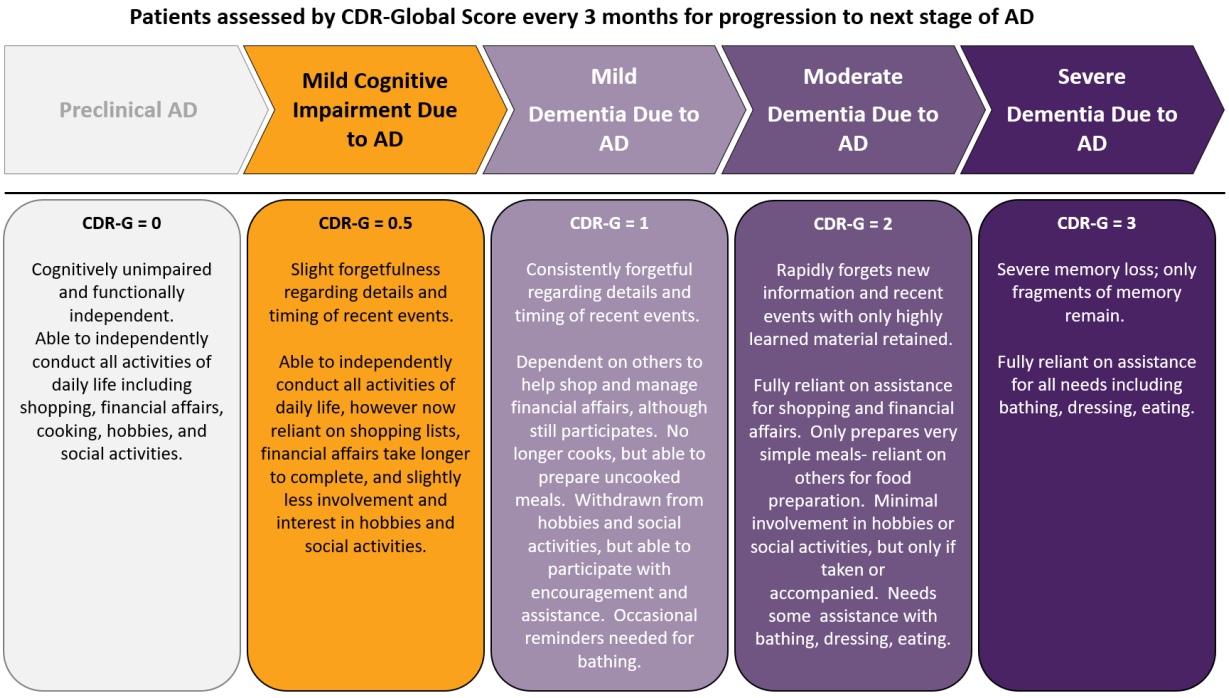
Figure 1.2. Primary and key secondary endpoints for the overall population, Study AACI.

Regarding the commonly used CDR-SB measure, Study AACI demonstrated the largest benefit seen in any randomized AD clinical trial conducted to date, both in absolute difference versus placebo (0.70) and in percentage slowing of progression versus placebo (29%), reinforcing the relationship between degree of plaque clearing and degree of clinical benefit now observed across a number of recent AD studies. Efficacy was consistent across subgroups for primary and key secondary clinical measures and was further supported by biomarkers relevant to disease modification.

Further data results for the program are summarized in Section 6.

Clinical meaningfulness: disease stage progression time-to-event analysis

Another way to contextualize the clinical meaningfulness of these results is to express them by estimating the delay of disease progression. Clinical staging of disease is assessed by the Clinical Dementia Rating Scale – Global (CDR-G) score and is described in Figure 1.3. Given the course of disease, the irreversible nature of neuronal loss, and the mechanism of action of donanemab targeting the removal of amyloid plaques, the primary expectation for amyloid-targeting therapies is to delay disease progression, that is, keeping patients at their current, earlier clinical stage of disease longer to preserve meaningful daily functioning longer.



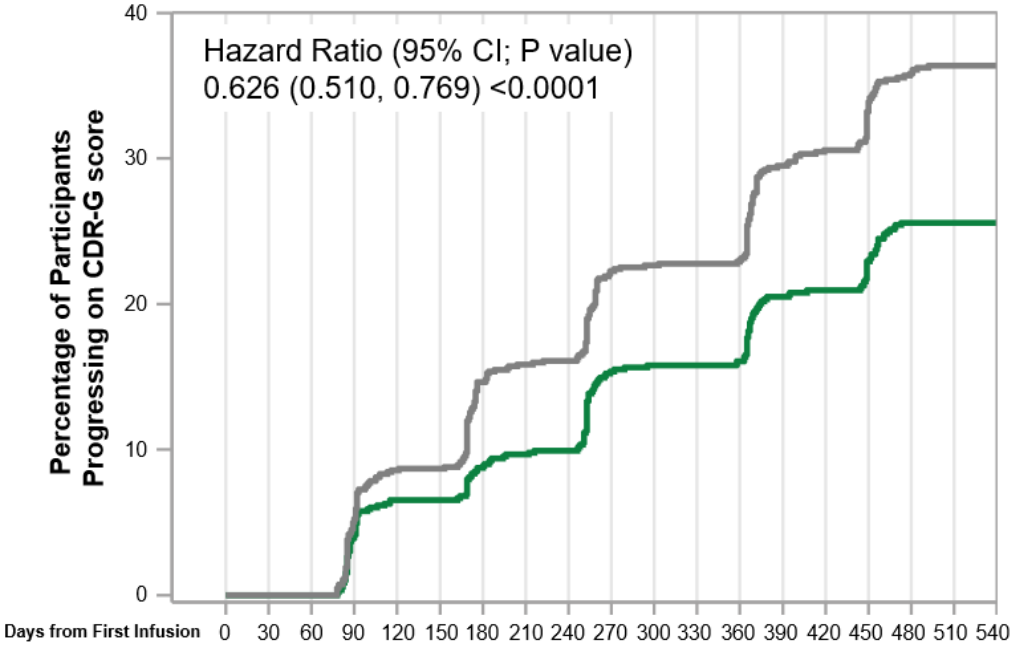
Abbreviations: AD = Alzheimer's disease; CDR-G = Clinical Dementia Rating Scale – Global score.

Figure 1.3. Alzheimer's disease clinical progression on CDR-G score.

In this prespecified, alpha-controlled analysis, advancement to the next clinical stage was determined in an event-driven analysis and defined as an increase in the CDR-G score at 2 consecutive visits. Patients were assessed every 3 months for progression to the next stage of AD and results showed that patients treated with donanemab demonstrated a significantly lower risk

of progression (hazard ratio [HR]: 0.63, p<0.0001; Figure 1.4). Delays in advancement to the next stage of disease are large and clinically meaningful changes for patients and caregivers resulting in more time spent at an earlier stage of the disease.

Additional information for clinically meaningful benefit is provided in Section 6.2.3.3.3.



Abbreviations: AACI = I5T-MC-AACI; CDR-G = Clinical Dementia Rating Scale – Global score; CI = confidence interval.

Note: Gray line indicates the placebo group and green line indicates the donanemab group. Hazard ratio and p-value were generated using a Cox proportional hazards model adjusted for baseline age, baseline value, and baseline acetylcholinesterase inhibitor/memantine use, and stratified by pooled investigator.

Figure 1.4. Risk of progression: CDR-G score (Overall Population), Study AACI.

Efficacy results support treatment of patients regardless of tau level

Donanemab-treated patients in Study AACI demonstrated consistent benefit across tau levels using the commonly used CDR-SB measure. While there is a numerically greater relative benefit observed in the low-medium tau compared to high tau population (36% and 21%, respectively), the absolute difference from placebo was similar across these subgroups (-0.67 and -0.69, for low-medium and high tau groups respectively) (Table 1.1).

Similarly, when evaluating the risk for individuals to progress as measured by the CDR-G score, almost identical reductions were observed for the low-medium and high tau subgroups (39% [HR 0.61] and 38% [HR 0.62] reduction of risk of advancing to the next stage of disease at 18 months, respectively) (Table 6.9). This benefit was observed despite the more aggressive disease and more rapid rate of progression for the high tau subgroup, thereby highlighting that there is a clinically meaningful impact at the patient level.

Note that Study AACI (with 100% tau imaging) was not powered to precisely estimate the effect size specifically within the smaller-sized high tau subgroup, and thus no formal statistical efficacy comparisons can be made between the low-medium and high tau populations (Section 6.2.3.3.6).

These findings are consistent with our biologic understanding that tau levels are prognostic of disease progression (with lower tau patients showing slower progression) but not predictive of absolute drug efficacy. While Lilly was the first to comprehensively demonstrate these phenomena, other sponsors have shown the same effect in the subset of patients where they have conducted tau imaging (Charil et al. 2024).

Collectively, data from AACI demonstrate that while patients with greater pathologic disease burden, as measured by high tau levels, are expected to have worse baseline cognition and function and likely poorer clinical outcomes overall, these patients can still benefit from amyloid-targeted therapy and should not be excluded from this potentially valuable treatment option.

Table 1.1. Efficacy across Tau Populations –Study AACI

	Overall		**Low-Medium Tau**		**High Tau[a]**	
	Placebo N = 876	**Donanemab N = 860**	**Placebo N = 594**	**Donanemab N = 588**	**Placebo N = 281**	**Donanemab N = 271**
CDR-SB (MMRM)						
Mean baseline	3.89	3.92	3.64	3.72	4.43	4.36
Change from baseline	2.42	1.72	1.88	1.20	3.34	2.64
Difference from placebo (95% CI) % slowing p-value	–	-0.70 (-0.95, -0.45) 29% p<0.001	–	-0.67 (-0.95, -0.40) 36% p<0.001	–	-0.69 (-1.19, -0.20) 21% p = 0.006
CDR-G Risk of Progressing[b]						
Reduced risk of advancing to the next stage of disease at 18 months (% risk reduction)	--	37% (p<0.0001)	--	39% (p<0.001)	--	38% (p = 0.004)

Abbreviations: AACI = I5T-MC-AACI; CDR-SB = Clinical Dementia Rating – Sum of Boxes; CI = confidence interval; MCID = minimal clinically important difference; MMRM = Mixed Model for Repeated Measures; N = number of patients in the population.

Note: Overall population consisted of patients with low-medium tau or high tau at baseline.

[a] High tau was a subpopulation that was not statistically powered in Study AACI.

[b] Time-to-event analysis (MCID).

The AACG and AACI studies did not enroll patients with no-very low tau because their early disease stage would not be predicted to progress meaningfully over the constrained 18-month study duration, thereby limiting the ability to show a clinical benefit versus placebo. To demonstrate the safety and key disease related biomarker changes within this subgroup, Lilly also conducted a separate Addendum to Study AACI that enrolled patients (n = 1053) solely based on confirmation of amyloid pathology, inclusive of patients known to be no-very low tau. Note that the no-very low tau pathology group (n=250) enrolled in this addendum represents the largest to-date characterization of this population treated with an amyloid-targeting therapy. In the no-very low tau population, there were positive treatment responses for key biomarkers, including amyloid, tau phosphorylated at threonine 217 (P-tau217), and glial fibrillary acidic protein. The magnitude of improvement in these disease relevant biomarkers were consistent with, or in some cases better than, those observed in patients with low-medium and high tau levels (Table 1.2). Importantly, this Addendum also demonstrated that the safety of donanemab in patients with no-very low tau levels was consistent with observations from the Phase 3 pivotal study (Table 6.24).

Table 1.2. Key Biomarker Results across Tau Groups, Donanemab-Treated Group, Study AACI, and Addendum

Percentage Change from Baseline at 76 Weeks	Tau Population/Subpopulation		
	No-Very Low Tau[a]	Low-Medium Tau[b]	High Tau[b]
Amyloid reduction (%)	86%	85%	80%
P-tau217 reduction (%)	56%	39%	33%
GFAP reduction (%)	22%	21%	18%

Abbreviations: GFAP = glial fibrillary acidic protein; P-tau217 = tau phosphorylated at threonine 217, also called phospho-tau 217.

[a] Patients enrolled in the addendum.

[b] Enrolled in placebo-controlled period.

Collectively, these results confirm that only amyloid pathology and assessment of other risk factors are needed for selection of patients with early symptomatic AD as appropriate candidates for consideration of an amyloid-targeted therapy.

Details of efficacy across tau populations are provided in Section 6.2.3.3.6.

Efficacy results support limited-duration dosing

Donanemab specifically binds to and removes insoluble brain amyloid plaques. Early clinical data for donanemab demonstrated deep and rapid clearance of brain amyloid in a high proportion of patients. Given the robust amyloid lowering achieved with donanemab, Lilly designed the donanemab program to allow patients to complete their course of treatment based on observed amyloid-imaging results, demonstrating the removal of brain amyloid plaque. As outlined below, observed data from the program supports labeling that allows clinicians and patients to consider stopping treatment once treatment-related amyloid clearance is achieved:

- Almost half of the patients achieved treatment-related amyloid clearance by Week 52 (Table 1.3).
- Following treatment completion, there was a slow reaccumulation rate of 2.8 Centiloids (CL) per year (Figure 5.1) and no rebound of amyloid plaque in the 12 months following treatment completion at 6 months (Figure 6.10).
- Notably, significant efficacy was observed at 18 months among patients that achieved early treatment-related amyloid clearance (that is, the collective group of patients eligible to move to placebo at either 6 months or 12 months) with continued widening of drug effect even after treatment was stopped (demonstrated by the numerically increasing difference between donanemab and placebo of CDR-SB among the patients that switched to placebo at 52, 64, and 72 weeks; Figure 1.5).

Based on this clinical trial design and these results, clinicians and patients should have the option to consider stopping treatment once treatment-related amyloid clearance is achieved.

Lilly has received consistent feedback from patients, caregivers, and healthcare professionals that this approach has the potential to decrease treatment burden, an important consideration for this vulnerable and elderly population. Payers, including the Centers of Medicare and Medicaid Services (CMS), have also expressed a great deal of interest in the potential for limited-duration dosing, as this may significantly lower the cost of care in comparison to chronically dosed medications. This approach also aligns with our mechanistic understanding of donanemab – primarily that once the target is cleared from the brain, continued dosing of donanemab is likely not beneficial and only adds to treatment burden and potential risks.

Lilly acknowledges that the decision to implement this limited treatment approach will be individualized in clinical practice and has recommended labeling that would provide flexibility to prescribing decisions. Of note, CMS recently implemented coverage policy changes that eliminate the limit on the number of amyloid PET scans per patient, allowing patients to access additional amyloid PET scans to evaluate for treatment response if desired.

Thus, the limited-duration dosing paradigm studied in the AACI program could be implemented in routine practice should patients, caregivers and their physicians decide to pursue it.

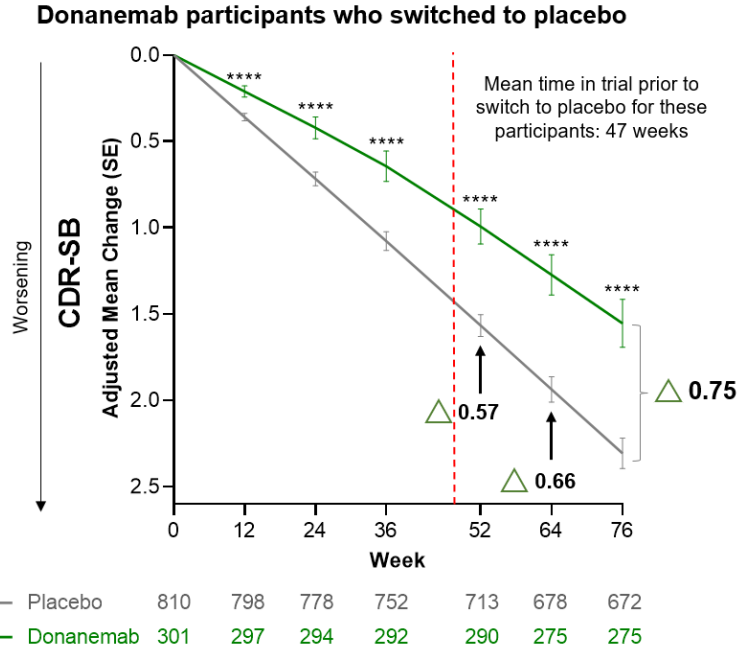
Finally, Lilly acknowledges that the design of the study, which did not randomly assign patients between continuous and limited therapy study groups, does not definitively quantify the effect of this intervention. Designing a study powered to do so would have been prohibitively large. However, the statistically significant and clinically meaningful efficacy results demonstrated in Study AACI reflect the implementation of this personalized approach and therefore should provide confidence to the scientific community as to the suitability of this approach.

Further data supporting a limited-duration treatment is summarized in Section 6.2.3.4.

Table 1.3. Percentage of Donanemab-Treated Patients Who Met the Reduction to Placebo Criteria Based on Amyloid PET, Study AACI

	Week 24	Week 52	Week 76
Overall population, % (n/N)	17.1 (130/761)	46.6 (313/672)	69.2 (429/620)

Abbreviations: AACI = I5T-MC-AACI; CL = Centiloid; n = number of patients in the specified category; N = number of patients in the population; PET = positron emission tomography.
Note: Less than 11 CL at 1 visit or less than 25 CL at 2 consecutive visits. Included patients from unscheduled visits at each time point.



Abbreviations: AACI = I5T-MC-AACI; CDR-SB = Clinical Dementia Rating Scale – Sum of Boxes; PET = positron emission tomography; SE = standard error.
Nominal p-values: ** p<0.01, *** p<0.001, **** p<0.0001.
Note: The mean time in the clinical trial prior to switch to placebo for these participants was 47 weeks, as shown by the red-dashed vertical line.

Figure 1.5. Efficacy results in patients who switched to placebo after treatment-related amyloid clearance at 6 or 12 months (CDR-SB, Overall Population), Study AACI.

1.7. Safety Results

Donanemab has a safety profile consistent with known amyloid-targeted therapy class risks.

The safety of donanemab was evaluated primarily in the placebo-controlled portion of the Phase 3 Study AACI and in the integrated placebo-controlled analyses inclusive of the Phase 2 Study AACG and Phase 3 Study AACI. Together, the integrated placebo-controlled analysis set,

referred to as placebo-controlled safety analysis population (Dona-PC), comprises 984 donanemab-treated patients.

A total of 2802 patients have received donanemab across the program (donanemab-treated integrated safety analysis population [All Dona]). This is the largest registration safety database to date for an amyloid-targeting therapy, providing 3470 patient-years of observation.

The safety findings from Study AACI, Dona-PC, and All Dona, regardless of the analysis approach, are similar and generally consistent with the safety profile for amyloid-targeting therapies. Mortality was extensively evaluated across the donanemab clinical program and is further discussed below. More safety data are summarized in Section 6.2.4.

Adverse events

In Dona-PC, treatment-emergent adverse events (TEAEs) were reported by 89% of donanemab-treated patients compared with 83% of placebo-treated patients. The most common AEs were amyloid-related imaging abnormalities (ARIA)–edema/effusions (ARIA-E; 24%), ARIA-hemorrhage/hemosiderin deposition (ARIA-H; 18%), COVID-19 (14%), fall (13%), and headache (13%)—consistent with other amyloid-targeted therapies. Serious AEs were reported by 17% of donanemab-treated patients compared with 15% of placebo-treated patients. The most frequently reported serious adverse events in the donanemab group were ARIA-E (1.5%), syncope (1%), pneumonia (1%), and COVID-19 (0.8%).

There were more discontinuations from study treatment and from study in the donanemab group, mainly due to infusion-related reactions (IRRs; 4%), ARIA-E (3%), superficial siderosis (1%), and ARIA-H (1%).

No clinically meaningful interactions by age, race, sex, ethnicity, or baseline tau level were observed between treatment groups on the frequency of common TEAEs.

ARIA

ARIA, manifested as ARIA-E and ARIA-H, are the primary on-target adverse effects of this generation of amyloid-targeting therapies.

Overall, ARIA-E was observed in 24% and ARIA-H in 31% of donanemab-treated patients in the Dona-PC analysis set (based on MRI or TEAE cluster). The majority of these were mild to moderate in radiographic severity, nonserious and asymptomatic. Symptomatic ARIA-E occurred in 6% and symptomatic ARIA-H occurred in 1% of patients treated with donanemab. Total serious ARIA-E or ARIA-H was 2%. Serious ARIA-E (for example, requiring hospitalization) was observed in 1.5% of patients and serious ARIA-H was observed in 0.4% of patients. Clinical symptoms associated with symptomatic and serious ARIA often included headache and confusion, with dizziness, nausea, and seizure reported less frequently. Three SAEs related to ARIA (0.3%) had a fatal outcome and were considered related to donanemab treatment.

Symptoms of ARIA were most often mild or moderate in severity. Most ARIA occurred by the sixth infusion or 24 weeks with most serious ARIA occurring by the third infusion or in the first

12 weeks (Figure 6.12). Median time to radiographic resolution for ARIA-E was 59 days (approximately 8 weeks).

Risk factors for ARIA included APOE ε4 carrier status with homozygotes exhibiting a higher frequency than heterozygotes, and heterozygotes greater than noncarriers. Other key risk factors for ARIA were identified from baseline magnetic resonance imaging (MRI) findings and include superficial siderosis and the number of microhemorrhages.

Intracerebral hemorrhage greater than 1 cm was uncommonly reported in donanemab-treated patients (0.3%) and placebo-treated patients (0.2%).

ARIA-E, ARIA-H, and macrohemorrhage were reported at a similar frequency in donanemab-treated patients, regardless of concomitant antithrombotic use within 30 days prior to the event.

While some have hypothesized that incidence of ARIA is related to rapidity or depth of plaque clearance, this is not supported by clinical trial data across molecules. In fact, Lilly conducted a head-to-head study comparing donanemab (n = 71) to another approved amyloid-targeting drug, aducanumab (n = 69), where significantly greater amyloid plaque clearance was achieved for the donanemab group at 6 months (-62.1 +/- 3.7 CL for donanemab compared with -16.4 +/- 3.8 CL for aducanumab) with a comparable frequency of total ARIA (25.4%) for donanemab-treated patients compared with aducanamab (26.1%). This relationship between treatment-related amyloid clearance and ARIA was maintained at 18 months (Section 6.2.4.6.1).

Infusion-related reactions

In donanemab-treated patients, IRRs were commonly observed (8.5%) and anaphylaxis was uncommonly observed (0.3%). Most of the IRRs were mild or moderate in severity (94%), occurred during the infusion or within 30 minutes and resolved the same day. Most patients experiencing an IRR reported an event within or by the fourth infusion. Serious hypersensitivity can be managed through appropriate labeling, including guidance for a 30-minute observation period following infusion, and a contraindication for those with known serious hypersensitivity to donanemab or excipients.

Mortality in donanemab clinical trials

AD is a progressive disease that is not currently possible to reverse and is ultimately fatal. Severe dementia frequently causes complications and other comorbid conditions and can significantly increase the risk of acute conditions that can cause death, such as pneumonia.

A comprehensive review and analysis of mortality was performed within the donanemab registration program. Regardless of the methodology, the findings are similar and conclusions are consistent. Beyond the known class-risk of ARIA with a low frequency of fatal events (0.3%), there is no evidence of an increase in risk of mortality or excess death related to donanemab.

Pre-specified Mortality Analysis

Mortality was initially evaluated according to the pre-specified integrated safety analysis plan in Dona-PC that accounted for adverse events leading to death occurring within the placebo-controlled period. This pre-specified approach, which is consistent with previous studies conducted in the early symptomatic AD space, considers a patient at risk for death from date of first dose through end of treatment period, or until study discontinuation. Using this approach, there were 18 (1.8%) deaths reported for donanemab-treated patients and 12 (1.2%) for placebo.

A comprehensive medical review for deaths occurring during the placebo-controlled period of the studies (Dona-PC) where cause of death as reported was performed. Three of the deaths in the donanemab population were considered related to donanemab treatment. Specifically, 2 events were reported as ARIA (1 ARIA-E and 1 ARIA-H) and 1 event reported as "Death" occurred in a patient with ongoing serious ARIA-E and ARIA-H. Beyond the 3 deaths associated with ARIA, no pattern or trend was reported in the type of event, timing, frequency, or nature of the events that led to death (Table 9.1). Most were a single type of event, each presenting with multiple risk factors. The causes of death appeared to be primarily explained by patient age, disease progression, comorbidities in patient medical history, and/or the use of confounding concomitant medications. The medical review of cases and conclusions are consistent irrespective of the methodology employed.

Beyond the placebo-controlled dataset, among any patient receiving donanemab (All Dona), the frequency of death reported using the pre-specified method in donanemab-treated patients (1.3%) was similar to the frequency observed in placebo-treated patients from the placebo-controlled period (1.2%) (Table 6.12). This demonstrates that as exposure to donanemab was expanded with patients from the separate addendum, the frequency of death did not increase.

Updated Mortality Analysis According to Most Recent FDA Feedback

Given that donanemab treatment duration was individualized in both AACG and AACI, a variety of different analyses were conducted to further clarify the mortality percentage across treatment groups in accordance with FDA requests. These analyses demonstrated broadly consistent results (Table 6.16).

In advance of this advisory committee meeting, the FDA proposed a methodology that considered any death that occurred during the timeframe from first dose to 76 weeks, irrespective of whether the patient was still on active treatment or had withdrawn from the study. In this analysis, fatal events were assigned to the initial treatment the patient received, even if the patient had completed treatment due to plaque clearance and was switched to placebo or if they had discontinued treatment or study entirely.

Responsive to FDA's requests and to further support this methodology, Lilly conducted a vital status assessment for AACI through a third-party for patients whose vital status was unknown at study completion (i.e., patients who were lost-to-follow up or had withdrawn from the study). This evaluation was limited to countries where follow up is legally permissible and to sites that agreed to this follow-up.

In total, vital status has been confirmed for 1555 of 1727 patients who received a dose of study drug in AACI, representing 90% of treated patients and providing reasonable resolution of any potential uncertainty for mortality analyses.

A summary of the vital status assessment is provided in Section 6.2.4.5. Importantly, none of the deaths in the donanemab group in this vital status assessment had ongoing ARIA at the last known MRI prior to loss-to-follow up or study withdrawal.

As of 09 May 2024, the majority of patients across both the donanemab and placebo treatment groups in AACI were alive.

- Incorporating vital status information into Dona-PC for all patients within 76 weeks of treatment, there were 20 (2.0%) deaths reported for donanemab-treated patients and 17 (1.7%) for placebo. Aside from the 3 ARIA-related deaths, there were 17 (1.7%) non-ARIA related deaths reported for donanemab-treated patients and 17 (1.7%) for placebo (Table 1.4).
- The cumulative incidence of death at 76 weeks was estimated using Kaplan-Meier methods and the Cox Proportional Hazards Model shows a HR (95% CI) of 1.2 (0.63 – 2.33) for all reported deaths and 1.0 (0.52-2.02) for non-ARIA related deaths (Figure 1.6).
- Thus, beyond the 3 deaths associated with ARIA, **there is no evidence of an increase in risk of mortality or excess death related to donanemab**.

There are limitations to this analysis including remaining missing information for 10% of the overall treated population in AACI. Causes of death for newly identified cases through this methodology are also not available for further medical review.

More information on mortality is summarized in Section 6.2.4.5.

Table 1.4. Risk of Fatal Outcomes Occurring Within 76 weeks

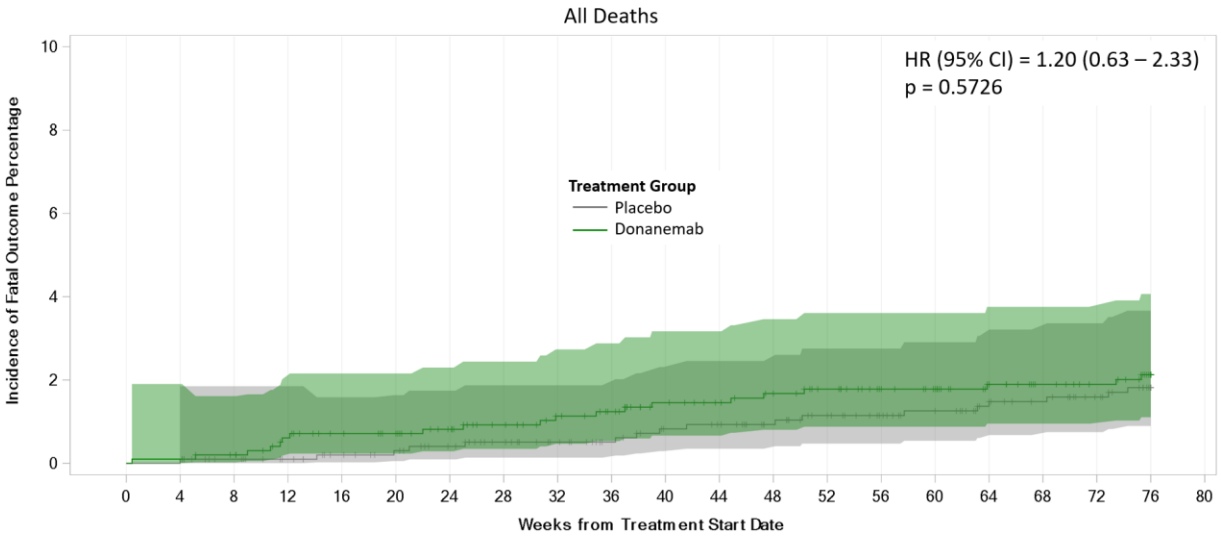
	AACI with vital status update		Dona-PC (AACG +AACI) with vital status update	
	Placebo (N = 874)	**Dona (N = 853)**	**Placebo (N = 999)**	**Dona (N = 984)**
Death				
N	16	19	17	20
Frequency (%)	1.8	2.2	1.7	2.0
95% CI	0.94, 2.72	1.24, 3.22	0.90, 2.50	1.15, 2.91
Risk difference (95% CI)	--	0.4 (-0.93, 1.73)	--	0.33 (-0.86, 1.52)
Odds ratio (p-value)[a]	--	1.22 (p = .611)	--	1.21 (p = .575)
ARIA-related Death				
N	0	3	0	3
Frequency (%)	--	0.35	--	0.3
95% CI	--	0.00, 0.75	--	0.00, 0.65
Risk difference (95% CI)	--	0.35 (-0.05, 0.75)	--	0.30 (-0.04, 0.65)
p-value	--	p = .120	--	p =.079
Non-ARIA related Death[b]				
N	16	16	17	17
Frequency (%)	1.8	1.9	1.7	1.7
95% CI	0.94, 2.72	0.97, 2.79	0.90, 2.50	0.91, 2.54
Risk difference (95% CI)	--	0.05 (-1.23, 1.32)	--	0.03 (-1.12, 1.17)
Odds ratio (p-value)	--	1.03 (p >.999)	--	1.02 (p = .953)

Abbreviations: AACI = I5T-MC-AACI; ARIA = amyloid-related imaging abnormality; CI = confidence interval; Dona = donanemab; LTE = long-term extension; n = number of patients with adverse event leading to death; N = number of patients in the treatment group; PC = placebo controlled.

[a] Mantel-Haenszel odds ratio stratified by study. Donanemab is numerator, placebo is denominator.

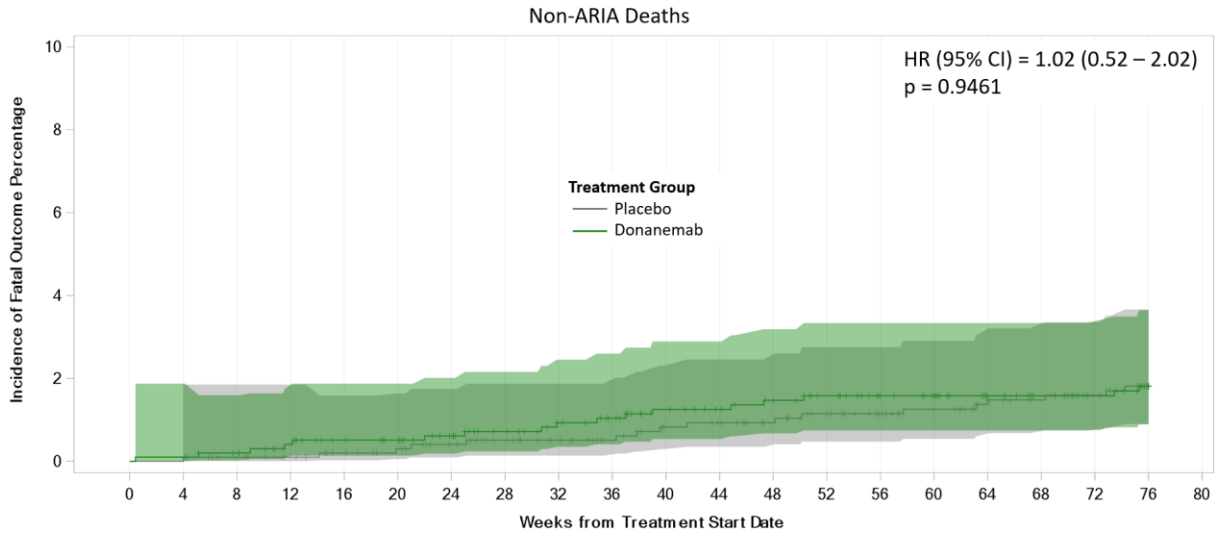
[b] Deaths related to ARIA in 3 patients in Study AACI were excluded.

Note: Participants were included from the first dose of treatment to 76 weeks irrespective of patient disposition and incorporated the results of vital status searches from Study AACI.



Cumulative Event Percentage (n at risk) at Selected Times(t) in Week

Treatment	N	Event	t = 8	t = 16	t = 24	t = 32	t = 40	t = 48	t = 56	t = 64	t = 72	t = 78
Placebo	999	17	1 (992)	2 (979)	4 (967)	5 (950)	8 (934)	9 (922)	11 (904)	14 (888)	15 (873)	17 (0)
LY3002813	984	20	2 (979)	7 (963)	8 (950)	11 (931)	14 (913)	16 (902)	17 (886)	18 (870)	18 (855)	20 (0)



Cumulative Event Percentage (n at risk) at Selected Times(t) in Week

Treatment	N	Event	t = 8	t = 16	t = 24	t = 32	t = 40	t = 48	t = 56	t = 64	t = 72	t = 78
Placebo	999	17	1 (992)	2 (979)	4 (967)	5 (950)	8 (934)	9 (922)	11 (904)	14 (888)	15 (873)	17 (0)
LY3002813	984	17	2 (979)	5 (963)	6 (950)	9 (931)	12 (913)	14 (902)	15 (886)	15 (870)	15 (855)	17 (0)

Abbreviations: ARIA = amyloid-related imaging abnormality, CI = confidence interval, HR = hazard ratio, n = number of patients.

Figure 1.6. Kaplan-Meier curves estimating cumulative incidence with hazard ratio and confidence intervals for death within 76 Weeks of Treatment, for All Deaths and Non-ARIA Deaths.

Risk Management

Based on the learnings about ARIA, including the 3 fatal ARIA-related cases from the clinical trials, recommendations for managing ARIA include the following:

- Labeling identifying patients at increased risk for ARIA, including testing for APOE ε4 status as well as those with baseline MRI findings consistent with cerebral amyloid angiopathy.
- Dose titration as part of standard dose posology.
- Monitoring MRI scans early in treatment with assessments prior to the second, third, fourth, and seventh infusion and for any symptomatic ARIA. Of note, the scan prior to the third infusion is proposed to be added to labeling after review of Study AACI data further clarified typical onset of serious ARIA.
- Dose interruption for radiographically moderate or severe, symptomatic or serious ARIA, and reassessment of benefit-risk
    - resume dosing after resolution or stability of MRI and symptoms (if present), or
    - permanent discontinuation of donanemab.
- Use of corticosteroids as appropriate for serious or symptomatic ARIA.

The review of clinical trial data shows an overall low frequency of fatal AEs, regardless of analysis methodology. The comprehensive medical review of the individual fatal cases confirmed an association between donanemab and ARIA-related deaths but does not suggest a possible causal association for remaining fatal events.

1.8. Benefit-Risk Summary

The target population for donanemab is patients with early symptomatic AD, that is, mild cognitive impairment and mild dementia due to AD.

The key benefit of donanemab is significant and clinically meaningful slowing of disease with positive impacts on both cognitive and functional decline across multiple clinical outcome measures of AD. This benefit was observed across all key clinical efficacy measures, including iADRS, CDR-SB, ADAS-Cog$_{13}$, and ADCS-iADL. The benefit is clinically meaningful as assessed by magnitude of effects, stability of disease, and significantly lower risk of progression. Treatment effects favoring donanemab were observed in all baseline tau participant groups, though greater efficacy was observed in patients with low-medium tau, suggesting that treating patients earlier provides more benefit. A positive benefit was also observed in the patients with high tau based on CDR-SB and CDR-G score, and in patients with no-very low tau based on biomarker data. These data further support that all patients with early symptomatic AD who have amyloid pathology would have a potential for a positive benefit. Supporting these efficacy results is the robust amyloid plaque clearance observed, which allowed a majority of patients to complete their course of treatment by the end of the study. The option to stop treatment when plaque is considered cleared is another benefit of treatment with donanemab. The results meet the regulatory precedent and substantial evidence standard for demonstration of efficacy for the proposed indication.

The key risks of donanemab are symptomatic ARIA and serious hypersensitivity, consistent with the class of amyloid-targeting therapies. Most ARIA events were nonserious and resolved (ARIA-E) or stabilized (ARIA-H) upon treatment discontinuation or therapeutic intervention, as needed. Symptomatic ARIA-E was observed in 5.8% of donanemab-treated patients in the placebo-controlled period. Some symptomatic ARIA required hospitalization (that is, serious ARIA) and 3 fatal events were reported. Beyond the 3 deaths associated with ARIA, no pattern or trend was reported in the type of event, timing, frequency, or nature of the events. A careful case-by-case analysis of all other non-ARIA-related deaths revealed no likely mechanism of action or causality associated with donanemab. Serious hypersensitivity reactions, including IRRs and immediate hypersensitivity reactions, were observed in 0.6% of donanemab-treated patients in the placebo-controlled period. These events were transient and resolved. Similar to efficacy benefits, the safety profile in patients with no-very low tau was consistent with patients with varying levels of tau (that is, low-medium tau and high tau).

The key risks can be mitigated through appropriate labeling and clinical monitoring, and further characterized through post-authorization studies. For ARIA, a schedule of baseline and monitoring MRI scans during early treatment is recommended, along with APOE testing. Additionally, guidance to prescribers on the suspension of dosing in response to ARIA events based on the severity of radiographic findings and clinical symptoms is recommended. For serious hypersensitivity reactions, observation during and briefly after infusion and appropriate treatment is recommended. Recognizing that randomized controlled studies cannot fully characterize rare or uncommon safety events due to limits in sample size and study duration and that post-authorization safety studies are better suited to further characterize the broader safety profile in a larger, more diverse, population, Lilly is proposing several post-authorization studies to further characterize the key risks.

Overall, given the seriousness of AD and the limited options for disease-modifying treatments, donanemab provides a clinically meaningful treatment benefit for patients with AD, and such a benefit is anticipated irrespective of baseline tau. The potential risks of donanemab, appropriately managed as instructed in labeling, are outweighed by the demonstrated benefits on the clinical endpoints in those with AD.

2. BACKGROUND ON ALZHEIMER'S DISEASE

Unmet Need

Treatment options that modify the underlying pathology of AD and slow the cognitive and functional decline associated with disease progression, are urgently needed, given the serious and ultimately fatal nature of AD, and the major burden for patients, caregivers, and public health.

2.1. Overview of Alzheimer's Disease

AD is an age-related, neurodegenerative disorder characterized by an inexorable progressive decline in cognitive and functional abilities. It is a serious and fatal disease. The number of people afflicted with AD worldwide is estimated at

- 32 million with AD dementia
- 69 million with MCI and mild dementia due to AD, and
- 315 million with preclinical AD (Gustavsson et al. 2023).

The clinical course of AD involves progressive memory loss, behavioral alteration, gait and motor disturbances, and declining ability to perform activities of daily living, eventually leading to complete dependence on a caregiver, usually followed by nursing home care (Bynum et al. 2004), and eventually death. No patients have ever recovered from AD, and the progressive loss of independence for patients with AD results in a tremendous burden to patients and to their caregivers, families, and to our society (Alzheimer's Association 2023).

In the brain, AD is characterized by the production and deposition of amyloid plaques. These plaques are an early and necessary signal in the pathogenesis of AD. Accumulation of plaques can begin decades before symptoms begin to show and can take decades to accumulate to pathological levels. As AD progresses, another protein, tau, accumulates and spreads across the brain. Increasing tau pathology correlates with worsening of cognition (Cho et al. 2019; Pontecorvo et al. 2019). Together, amyloid plaques and tau pathology damage neuronal cells and because neuronal cell loss is likely irreversible, early intervention in this disease cascade is critical to preserve as much cognition and function as possible for patients.

2.2. Current Treatment Options for Alzheimer's Disease

There is an urgent unmet need to identify disease-modifying therapies for patients with AD that offer an early intervention to preserve patient cognition and function and change the trajectory of the disease. Currently, there is only 1 disease-modifying therapy, lecanemab, another amyloid-targeted antibody, approved and marketed in the United States. However, one available therapy is not sufficient. Patients, caregivers and providers deserve multiple disease-modifying options to treat this complex, progressive disease. This is especially important given the serious and ultimately fatal nature of AD, and the major public health burden for patients, caregivers, and society. Donanemab offers meaningful clinical benefit with a potential to stop treatment when treatment-related amyloid clearance is achieved, and provides an additional and clinically important disease-modifying treatment for Alzheimer's patients.

3. DONANEMAB PRODUCT DESCRIPTION

Donanemab mechanism of action

Donanemab is an immunoglobulin gamma 1 mAb directed against insoluble, modified, N-terminal truncated pyroglutamate form of amyloid beta present only in brain amyloid plaques (Bridel et al. 2017). Donanemab binds to the deposited amyloid plaque and aids its removal through microglial-mediated phagocytosis (DeMattos et al. 2012).

3.1. Donanemab Proposed Indication and Dosing

Proposed indication

Donanemab is intended for use in patients with early symptomatic AD, including those with MCI or mild dementia stage of AD.

Proposed dosing

Confirm the presence of amyloid beta pathology prior to initiating the treatment. The recommended dosage of donanemab is 700 mg administered as an IV infusion Q4W for the first 3 doses, followed by 1400 mg Q4W. Consider discontinuation of donanemab once treatment-related amyloid clearance is achieved.

4. REGULATORY AND DEVELOPMENT HISTORY

The regulatory history of donanemab includes:

- July 2018 and June 2021: Fast Track and Breakthrough Therapy designations, based on the potential to treat a serious condition and offer a substantial improvement over available therapy
- May 2022: submission for Accelerated Approval, based on the registration-quality Phase 2 study (TRAILBLAZER-ALZ; AACG)
- January 2023: Complete Response, due to lack of sufficient 1-year exposures; no other deficiencies were noted
- June 2023: Class 2 Resubmission for traditional approval, based on the Phase 3 study (TRAILBLAZER-ALZ 2; AACI)
- October 2023: Major Amendment, for additional FDA review time of newly requested safety analyses

4.1. Clinical Development Program

Figure 4.1 and Table 4.1 provide details on the donanemab clinical program with descriptions of the studies that support registration.

Abbreviations: AACG = I5T-MC-AACG; AACI = I5T-MC-AACI.

Figure 4.1. Overview of key donanemab clinical studies.

The clinical efficacy of donanemab in slowing disease progression is based on the placebo-controlled results from the Phase 3 Study AACI, with supportive evidence from the Phase 2 Study AACG. The safety profile of donanemab is predominantly based on the integrated placebo-controlled safety results of Studies AACI and AACG, with support from the LTE of AACI, a separate ongoing Addendum to AACI, an ongoing extension study for AACG (Study AACH), and an ongoing active-comparator Study AACN.

Table 4.1. Listing of Donanemab Clinical Studies to Support the Biologics License Application

Identifier and Description	Cohort, *Status*	Role in Labeling
AACI (TRAILBLAZER-ALZ2) Multicenter, randomized, double-blind, placebo-controlled, Phase 3 study of donanemab in patients with early symptomatic AD with the presence of brain amyloid and low-medium or high tau levels.	AACI, *Completed*	Placebo-controlled primary outcome cohort with a 76-week DB period, contributing up to 72 weeks of study treatment, to assess clinical pharmacology, efficacy, and safety outcomes.
	AACI-LTE, *Ongoing*	Long-term safety extension for patients who completed the PC period, contributing up to 72 weeks of donanemab exposure, to assess safety outcomes (included in IDB only). The efficacy and clinical pharmacology biomarker data remain blinded.
	Addendum, *Ongoing*	Direct enrollment of treatment-naïve patients based on amyloid pathology, open-label addendum, contributing up to 72 weeks of donanemab treatment, to assess safety outcomes (IDB only). The clinical pharmacology biomarker data remain pending until study completion. The addendum does not include any clinical efficacy assessment.
AACG (TRAILBLAZER-ALZ) Registration-quality, multicenter, randomized, double-blind, placebo-controlled, Phase 2 study of donanemab in patients with early symptomatic AD and low-medium tau levels.	AACG, *Completed*	Placebo-controlled cohort with a 76-week DB period, contributing up to 72 weeks of study treatment, to assess clinical pharmacology, efficacy, and safety outcomes.

Abbreviations: AACI = placebo-controlled period of Study AACI; AD = Alzheimer's disease; DB = double blind; Dona = donanemab; IDB = integrated database; LTE = long-term extension.

Summary of tau in donanemab development program

Study AACG (Phase 2)

- Enrolled amyloid-positive patients with low-medium tau levels to ensure a homogeneous and well-balanced clinical trial, given the modest overall sample size.
- Patients with no-very low tau were excluded because they potentially would not progress meaningfully over the study duration while patients with high tau were excluded because of potentially too fast progression during the study period.

- This study (see Section 6.1) demonstrated clinical benefit of donanemab treatment with significant slowing of disease progression among patients who were amyloid positive. Of note, this was the first disease-modifying clinical trial in AD to demonstrate a positive outcome on a primary endpoint of cognition and function.

Study AACI (Phase 3)

- Expanded eligibility to include amyloid-positive patients with high as well as low-medium tau levels.
- Given the prognostic value of tau, patients were stratified by level to ensure balance between the treatment groups. Patients with no-very low tau were not included since their lower probability of decline during the 18-month study period reduces their ability to contribute to the study's power to measure the potential drug effect.
- High-tau patients were included as part of the overall treatment population; the high-tau subpopulation was not separately powered for demonstration of efficacy. As a result, the study included 2 prospective populations to assess efficacy benefit: 1) the overall study population, and 2) the low-medium tau population consistent with the Phase 2 study population for replication of results.
- The prespecified statistical tests were designed to demonstrate efficacy benefit in the overall population irrespective of tau pathology. Efficacy in the overall population supports that testing for tau pathology is not required in clinical practice.

5. OVERVIEW OF CLINICAL PHARMACOLOGY

Clinical Pharmacology Summary

- PK and PD results support the proposed recommended dosing regimen, including the option for prescribers to potentially stop treatment based on amyloid pathology.
- Amyloid plaque reaccumulation is slow at 2.8 CL per year.
- Patients who completed active treatment by 6 months are not expected to become amyloid positive for up to 5 years.

5.1. Pharmacokinetics

Absorption

Donanemab is administered by IV infusion and C_{max} is achieved at the end of infusion.

In a pilot evaluation of subcutaneous bioavailability (Study I5T-MC-AACC), at a dose of 3 mg/kg, bioavailability was approximately 60% and time of maximum observed drug concentration occurred approximately 5 days after administration of a single dose of subcutaneous 3 mg/kg donanemab. It is unknown whether a similar bioavailability would be observed at higher dose.

Distribution

Following IV administration, donanemab PK follows a biphasic profile, consistent with 2-compartment PK. Based on the population PK analysis, central volume of distribution is 3.36 L, with 18.7% interindividual variability, whereas peripheral volume of distribution is 4.83 L, with 93.9% interindividual variability.

In Phase 1 studies, the ratio of cerebrospinal fluid to serum concentrations of donanemab was approximately 0.2%, which is consistent with other monoclonal antibodies (Yu and Watts 2013).

Metabolism and elimination

Donanemab is a mAb and is expected to be degraded into small peptides and amino acids via catabolic pathways in the same manner as an endogenous immunoglobulin G; hence, there is no active metabolite formation or metabolic inhibition or induction of enzymatic pathways. It is also not expected to be metabolized by the CYP450 families of drug-metabolizing enzymes responsible for metabolism and elimination of small molecules and would, therefore, not cause CYP450-mediated clinical drug–drug interactions as a victim drug.

Based on the population PK analysis, clearance is 0.0255 L/h, with 24.9% between-participant variability. Half-life is approximately 12.1 days.

Dose proportionality and time dependence

In doses from 10 mg/kg to 40 mg/kg, $AUC_{(0-\infty)}$ and C_{max} were approximately dose proportional following single doses. At doses of 10 mg/kg and 20 mg/kg, $AUC_{\tau,ss}$ and $C_{max,ss}$ were approximately dose proportional at steady state.

The PK of donanemab appears to be time linear at the 10 to 20 mg/kg dose levels. No accumulation of donanemab was observed with the 10 mg/kg Q4W dose, as shown by the accumulation rate of approximately 1. There was limited accumulation with donanemab 20 mg/kg Q4W, with a mean accumulation rate of 1.26. Additionally, the C_{max} and AUC_{τ} at Day 1 and at steady state (Days 127 and 141), in the same participant, following 10 or 20 mg/kg Q4W regimens, in general, appeared to be similar.

Effect of intrinsic factors on donanemab PK

The impact of intrinsic factors on exposure was not considered clinically meaningful, as there did not appear to be a significant impact on plaque reduction and other clinical outcomes at the proposed dosing regimen.

Specifically, donanemab PK was not influenced by

- age (54 to 88 years at study entry)
- gender (55.0% female)
- race (89.9% White, 6.3% Asian, 2.9% Black, 0.3% American Indian or Other)
- Cockroft-Gault creatinine clearance (8.1 to 179.9 mL/minute), or
- APOE ε4 carrier status (66.4% positive).

Body weight

Body weight was identified as a significant covariate on total body and distributional clearances, as well as central and peripheral volumes of distribution. Body weight increases clearance and volume of distribution following typical allometric relationships (exponent of 0.8 for clearance terms and exponent of 1 for volume terms). Accordingly, heavier patients are expected to have higher clearance, higher volume of distribution, and lower overall exposure. In general, the clinical relevance of body weight on exposure is expected to be minimal. Changing from weight-based dosing to flat dosing resulted in modest increase in $C_{max,ss}$ variability, but no meaningful changes in $AUC_{\tau,ss}$ or trough concentrations were observed at steady state. Because both approaches performed similarly, flat dosing is recommended for donanemab.

ADA titer

Donanemab clearance was found to increase with ADA titer. The population PK/PD analysis showed that at the highest titer (1:5242880), median clearance increased by maximum of 39% compared with median clearance at low titer group (below 1:5120; titer of 1:5). This increase in clearance with titer resulted in a 17% decrease in $AUC_{\tau,ss}$ and a 31% decrease in drug concentration before the next dose ($C_{trough,ss}$), comparing low (below 1:5120) to high titer group (above 1:20480). Titer had no appreciable impact on $C_{max,ss}$. Immunogenicity had no impact on ARIA-E and clinical efficacy. Irrespective of ADA, sufficient exposure was achieved, and significant plaque reduction was observed. The clinical impact of immunogenicity is more fully described in Section 5.3.

5.2. Pharmacodynamics

The target PD activity of donanemab is to reduce amyloid plaque. As part of the population PK/PD analysis, the effect of donanemab treatment on amyloid plaque was examined using analyses of amyloid PET.

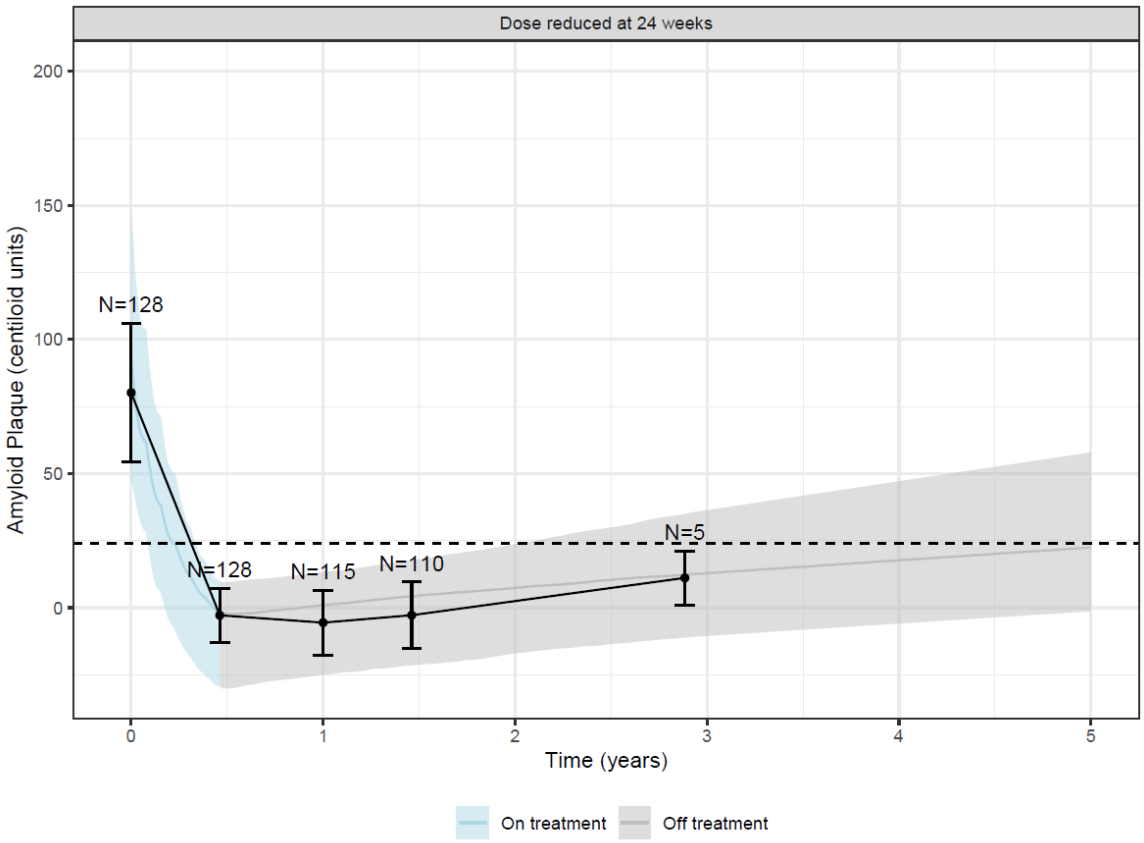
Exposure–amyloid plaque relationships
An exposure-response analysis described the relationship with amyloid reduction as measured using amyloid PET. Treatment effect was associated with maintaining serum donanemab concentrations above a median (95% CI) threshold concentration of 15.2 μg/mL (8.54, 18.0). No covariate effects, including APOE ε4, ADA titer, and baseline tau burden influencing amyloid removal, were identified. Clearance increases with increasing ADA titer, but the vast majority of patients (above 95%), including those with high titer, maintained average concentrations above the threshold efficacy concentration throughout the interdosing interval.

All observed longitudinal amyloid plaque observations from N = 2023 were used together with individual patients' dosing histories and exposure, including off-treatment individual patient amyloid plaque. The impact of completing active treatment on plaque reaccumulation was investigated by simulations using treatment exposure-response (amyloid plaque) relationship using previously established methods (Shcherbinin et al. 2022; Gueorguieva et al. 2023b). Data were available with longest off-treatment duration of 28 months and specifically:

- Study AACH (Part C), N = 15 patients with mean off-treatment period duration of 22 months (range of 15 to 28 months), and
- Study AACI, N = 256 with mean off-treatment period duration of 8 months (3 to 14 months).

Observed amyloid plaque data from Study AACI patients in whom plaques were cleared at Weeks 24 and 52 and were switched to saline infusions are discussed in Section 6.2.3.3.3. Amyloid plaque levels, once cleared with donanemab treatment, remained low until the end of Study AACI at Week 76.

The amyloid reaccumulation rate (median, 95% CI) was estimated at 2.80 (2.16, 3.11) CL per year, with no evidence of rebound amyloid plaque accumulation. These findings are supported by natural accumulation modeling studies (Jagust et al. 2021), showing approximately 3.3 CL per year as the estimated rate of the natural amyloid accumulation. This places amyloid-cleared donanemab patients on the same amyloid plaque accumulation trajectory as amyloid-negative individuals, where projected time to become amyloid positive was, on average, 5 years (Figure 5.1).



Abbreviations: CL = Centiloid; N = number of patients.
Simulated amyloid plaque level over time using treatment exposure-response model and stratified by patients achieving <11 CL by 24 weeks and then discontinuing donanemab treatment; shaded region indicates 90% prediction interval (includes between-participant variability), solid line is predicted median, blue region depicts patients on treatment (to Week 24) and then off-treatment (gray region); dashed black reference line shows 24.1 CL. Observed mean (standard deviation) are shown by the solid back line and bar plot.

Figure 5.1. Amyloid plaque level over time using treatment exposure-response model and stratified by patients achieving <11 CL by 24 weeks and then discontinuing donanemab treatment.

Exposure–clinical efficacy relationship

The donanemab disease progression model established initially using Study AACG (Gueorguieva et al. 2023a; Shcherbinin et al. 2022) and natural disease progression model in AD (Gueorguieva et al. 2022) evaluated the impact of donanemab exposure–clinical efficacy relationship. This model-based evaluation provided an understanding on disease progression rate (placebo and treatment groups), baseline score, and treatment effect, and allowed for identification of significant covariates. Treatment effects favoring donanemab were observed in all baseline tau participant groups. ADA titer and body weight had no statistically significant impact on the effect of donanemab treatment.

Simulations with the disease progression model suggest that slowing of disease progression increases over time compared with placebo. Simulation results suggest that once amyloid is cleared, there is little impact of stopping treatment on clinical efficacy. This is due to the very slow reappearance of amyloid once it has been removed by donanemab treatment. Limitations of disease progression analysis were that the model was built only on data that explored a single-dosing regimen with a relatively narrow range of exposures.

Exposure–ARIA-E relationship

Factors impacting first occurrence of ARIA-E based on MRI or TEAE cluster were evaluated using time-to-event analyses (Gueorguieva et al. 2023b). ARIA-E risk was primarily driven by APOE ε4 genotype (3.9 times higher in homozygotes compared with noncarriers). Additionally, but to a smaller extent by number of baseline microhemorrhages (1.039 times higher in patients with 2 microhemorrhages compared with 1 or 0 microhemorrhages at baseline). No statistically significant impact of immunogenicity, age, gender, race, baseline tau, antithrombotic medication, and body weight was noted on the risk of ARIA-E. The analysis used data from Studies AACG and AACI, both of which examined a single-dosing regimen.

5.3. Immunogenicity

In up to 18 months of treatment, 88% of patients developed treatment-emergent ADA.

The presence of ADA increased donanemab serum clearance. However, irrespective of ADA, sufficient exposure was achieved, and significant plaque reduction was observed.

The potential impact of ADA on iADRS and CDR-SB was assessed in the exposure-efficacy relationship (described previously) and in a repeated-measures model. Both analyses demonstrate that there was no clinically significant effect of ADA on the effectiveness of donanemab.

ADA formation and titer was associated with a higher incidence of IRRs. However, 92% of patients with ADA and 67% of patients with high titer ADA (representing approximately 14% of patients) did not experience an IRR.

No association was observed between ADA and anaphylactic reactions, serious or severe hypersensitivity reactions, ARIA-E, or death.

In summary, ADA does not substantially impact the overall positive benefit-risk balance of donanemab.

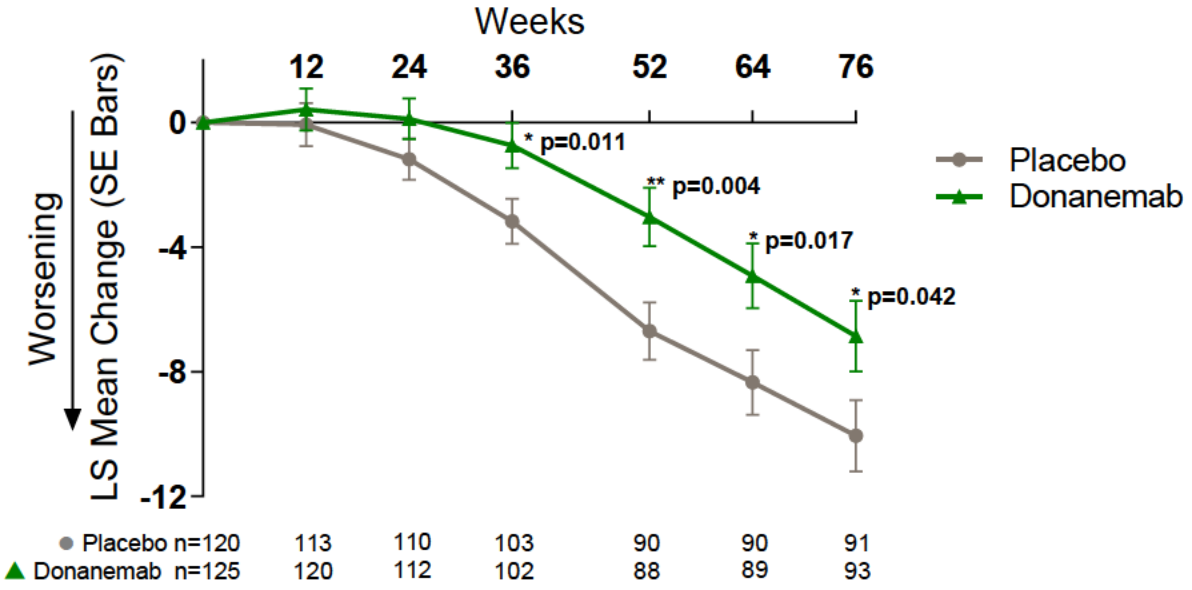
6. CLINICAL STUDY RESULTS

6.1. Phase 2 Results

The Phase 2 (Study AACG) efficacy results are not a focus of this Advisory Committee meeting. Primary efficacy endpoint results in Study AACG are provided in this subsection to demonstrate replication of positive primary endpoint results in the Phase 3 (Study AACI) study (Section 6.2.3.3.1).

Phase 2 (Study AACG) primary efficacy results

At Week 76, donanemab-treated patients had statistically significantly less decline in cognition and function than placebo-treated patients as assessed by the iADRS, thus meeting the primary objective of the study. The LS mean change difference ± SE was 3.20 ± 1.56 (p = 0.042). The analysis shows an approximately 32% reduction in cognitive and functional decline for donanemab-treated patients compared with placebo treatment. The MMRM analysis also showed statistically significantly lesser decline in cognition and function in donanemab-treated patients than placebo-treated patients at the Weeks 36, 52, and 64 time points.



Abbreviations: AACG = I5T-MC-AACG; iADRS = integrated Alzheimer's Disease Rating Scale; LS mean = least squares mean; MMRM = Mixed Model for Repeated Measures; n = number of patients in the specified category; SE = standard error.

Figure 6.1. MMRM analysis of change from baseline on iADRS, Study AACG.

The results of the secondary clinical endpoints in Study AACG are summarized in Table 6.1.

Table 6.1. Clinical Results of Secondary Endpoints at Week 76, Study AACG

Measure	Difference from Placebo (SE)	95% CI	p-Value[a]	Percent Slowing
CDR-SB	-0.36 (0.239)	-0.83, 0.12	0.139	22.6%
ADAS-Cog$_{13}$	-1.86 (0.898)	-3.63, -0.09	0.040	38.9%
ADCS-iADL	1.21 (1.009)	-0.77, 3.20	0.230	23.4%
MMSE	0.64 (0.525)	-0.40, 1.67	0.227	21.3%

Abbreviations: AACG = I5T-MC-AACG; ADAS-Cog$_{13}$ = Alzheimer's Disease Assessment Scale – 13-item Cognitive Subscale; ADCS-iADL = Alzheimer's Disease Cooperative Study – instrumental Activities of Daily Living subscale; CDR-SB = Clinical Dementia Rating Scale – Sum of Boxes; CI = confidence interval; MMSE = Mini-Mental State Examination; SE = standard error.

[a] p-Values not adjusted for multiplicity.

6.2. Phase 3 Results

6.2.1. Study Design

Study AACI is a multicenter, randomized, parallel-group, double-blind, placebo-controlled, Phase 3 study of donanemab in patients with early symptomatic AD.

Eligible patients were randomly assigned in a 1:1 ratio to receive either placebo or donanemab. Patients were randomly assigned to treatment groups by a computer-generated random sequence using an interactive web-response system. Randomization was stratified by investigative site and tau pathology (low-medium versus high).

The study included a screening period of up to 9 weeks, a treatment period of up to 72 weeks with final evaluations occurring 4 weeks later at Week 76, and a 48-week immunogenicity and safety follow-up period.

AACI Study Design	
Size	1736 randomly assigned patients
Geographies	Australia, Canada, Czech Republic, Japan, the Netherlands, Poland, the United Kingdom, and the United States
Dosing	• Donanemab: 700 mg IV Q4W for the first 3 doses and then 1400 mg IV Q4W, or • Placebo: placebo IV Q4W. Once treatment-related amyloid clearance criteria were achieved, donanemab-treated patients received a reduction to placebo in a blinded manner.
ARIA-related discontinuation rules	Treatment may be permanently discontinued in patients with treatment-emergent ARIA-E, ARIA-H, or both at the discretion of the principal investigator depending on the severity of clinical and radiologic findings.
Extension study	Seamless extension of up to 78 weeks
Additional donanemab exposures	Addendum (1047 patients received at least 1 dose of donanemab; tau PET not required, no tau exclusion criteria)

6.2.1.1. Entry Criteria

Inclusions

Study AACI enrolled a broad population of patients with early symptomatic AD and the presence of brain amyloid and tau pathology.

AACI Inclusion Criteria	
Age	Male and female patients, 60 to 85 years of age, inclusive, at the time of signing the informed consent.
Clinical staging	
Progressive decline in memory	Gradual and progressive change in memory function reported by the participant or informant for at least 6 months.
Clinical status	MMSE score of 20 to 28 (inclusive) • mild AD (Score 20-26) MCI (Score 27-28)
AD pathology	
Amyloid pathology	Meet amyloid PET scan (central read) criteria • greater than or equal to 37 CL
Tau pathology	Meet tau PET scan (central read) criteria • low-medium tau • high tau
Symptomatic AD medication	Stable concomitant symptomatic AD medications and other medications that may impact cognition for at least approximately 30 days prior to randomization

Methodology for Alzheimer's disease pathology determination

Amyloid pathology

Amyvid® (florbetapir F 18) was approved by the US FDA as a radioactive diagnostic agent indicated for PET imaging of the brain to estimate β-amyloid neuritic plaque density in adult patients with cognitive impairment who are being evaluated for AD and other causes of cognitive decline. A negative Amyvid scan indicates sparse to no neuritic plaques, and is inconsistent with a neuropathological diagnosis of AD at the time of image acquisition; a negative scan result reduces the likelihood that a patient's cognitive impairment is due to AD. A positive Amyvid scan indicates moderate to frequent amyloid neuritic plaques; neuropathological examination has shown this amount of amyloid neuritic plaque is present in patients with AD but may also be present in patients with other types of neurologic conditions as well as older people with normal cognition.

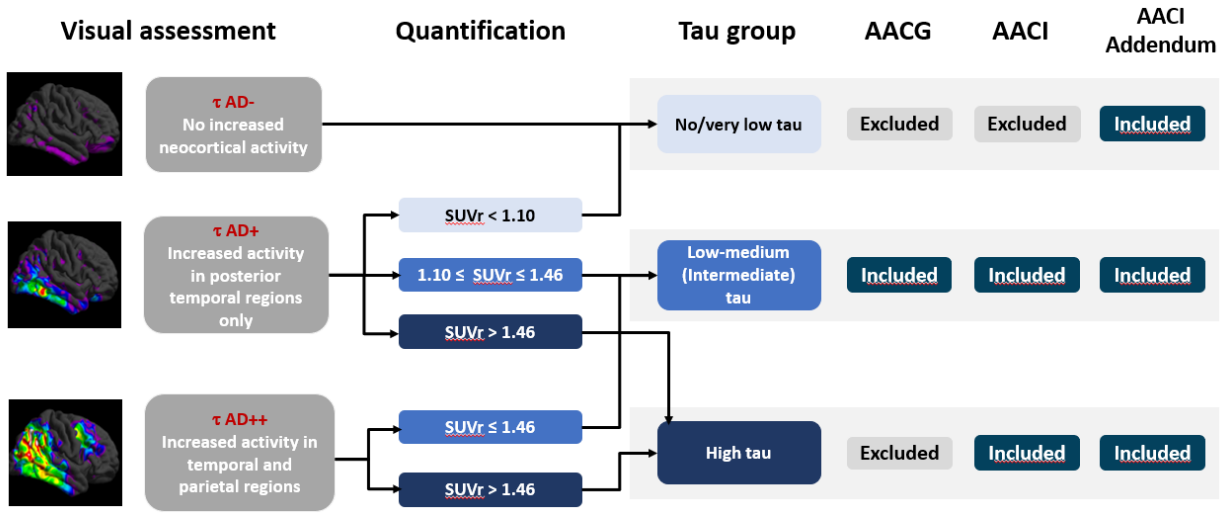
Tau pathology

Section 1.4 summarizes the approach for tau characterization in the program.

Tau PET levels at baseline were defined using a combination of visual and quantitative assessments (Figure 6.2).

Tauvid® (flortaucipir F 18) was approved by the US FDA as a radioactive diagnostic agent indicated for PET imaging of the brain to estimate the density of aggregated tau neurofibrillary

tangles in adult patients with cognitive impairment who are being evaluated for AD. Although the quantitative methods used in Study AACI have been implemented at multiple centers for research purposes, commercial software that implements these quantitation methods is currently not approved. There is currently no standardization or harmonization across centers or tracers for the quantitation of tau PET scans. Thus, the assessment of tau levels is neither standardized nor widely available in routine clinical practice such that any tau-based requirement to select a patient based on a specific tau level (for example, low-medium or high) is not feasible.



Abbreviations: MUBADA = multi-block barycentric discriminant analysis; PERSI = parametric estimation of reference signal intensity; SUVr = standardized uptake value ratio (based on MUBADA with PERSI reference region).

Figure 6.2. Tau assessment in Study AACI and Addendum.

Exclusions

Patients were excluded from the study if they had any contraindications for MRI or PET, or were sensitive to florbetapir F 18, florbetaben F 18, or flortaucipir F 18. Patients were also excluded if central read of screening MRI showed the presence of

- ARIA-E
- more than 4 cerebral microhemorrhages
- more than 1 area of superficial siderosis
- any macrohemorrhage (intracerebral hemorrhage greater than 1 cm), or
- severe white matter disease.

Patients with no-very low tau pathology were excluded from Study AACI (Figure 6.2) because their rate of disease progression was not expected to allow for reliable measurement of clinical decline or study treatment effects within the constrained 18-month study duration.

Dosing and treatment duration

Patients received one of the following treatments for up to 72 weeks:

- **Donanemab:** IV donanemab 700 mg Q4W for the first 3 doses, then 1400 mg Q4W
- **Placebo:** IV placebo Q4W

Limited-duration treatment option

Donanemab specifically binds to and removes brain amyloid plaques. Once the pharmacological target (insoluble amyloid plaque) is cleared from the brain, continued dosing of donanemab is likely not beneficial and only adds to treatment burden.

A quantitative approach to treatment completion was employed to improve the scientific certainty for research purposes of amyloid plaque reduction and to enable the ability to quantitate values of amyloid reduction results. Donanemab-treated patients therefore received a reduction to placebo based on the following predefined amyloid-imaging criteria at Week 24, 52, or 76:

- less than 11 CL at any single time point, or
- less than 25 CL at 2 consecutive time points.

Dose modification for patients who developed ARIA

For patients who developed ARIA during the titration period (that is, before the fourth infusion of study drug of the AACI placebo-controlled period or of the extension period), the investigator could decide to

- temporarily suspend dosing, then determine if the participant needed to remain on the presuspension dose (700 mg/placebo equivalent) either temporarily beyond the first 3 doses or throughout the remainder of the treatment period
- continue the same dose (700 mg/placebo equivalent) either temporarily beyond the first 3 doses or throughout the remainder of the treatment period, or
- continue the dosing schedule.

6.2.1.2. Assessments

6.2.1.2.1. Clinical

Clinical endpoints

The key endpoint measures evaluated to demonstrate efficacy and proposed for labeling are established measures of clinical outcomes and behavioral symptoms associated with AD dementia. These endpoints are considered appropriate assessments for a population with early symptomatic AD.

All key endpoints were assessed in the placebo-controlled analysis set. Strong control for type I error was prespecified in a graphical testing scheme (Figure 9.1).

Primary endpoint

- Change from baseline in the iADRS at 76 weeks

Key secondary endpoints

- Change from baseline in the CDR-SB at 76 weeks
- Change from baseline in the ADAS-Cog_{13} at 76 weeks
- Change from baseline in the ADCS-iADL at 76 weeks

Other important endpoints included in graphical testing scheme

- Disease progression time saved at Week 76 as measured by the iADRS
- Disease progression time saved at Week 76 as measured by the CDR-SB
- Difference in hazard of progressing to first meaningful clinical worsening event defined by the CDR-G
- Difference in probability of "no progression" as defined by the CDR-SB at Week 52

iADRS

The iADRS is a relatively new measure that integrates assessment of cognition and daily function. It is a summation of scores on 2 other widely used measures (ADAS-Cog_{13} measuring cognition and ADCS-iADL measuring function). These 2 measures are accepted as coprimaries in AD clinical trials. The iADRS captures clinical progression across the AD continuum from MCI due to AD through moderate dementia due to AD, and treatment effects have been demonstrated across MCI and mild dementia due to AD (Mintun et al. 2021). The iADRS score ranges from 0 to 144 with lower scores indicating greater impairment.

The iADRS has been validated (Wessels et al. 2015, 2018a) and its statistical properties have been described. Minimal clinically important change estimates for the iADRS have been defined (Wessels et al. 2022b), allowing for the assessment of MWPCs on the iADRS and to analyze risk of MWPC for patients on placebo compared with donanemab. Furthermore, iADRS scores are associated with meaningful outcomes of disease such as caregiver burden and quality of life (Wessels et al. 2022a).

CDR

The CDR (Hughes et al. 1982; Morris 1993) is a global assessment tool that can be used to effectively evaluate both cognition and function. The tool was initially developed to measure dementia severity and covers 6 categories or "boxes": Memory, Orientation, Judgment and Problem Solving, Community Affairs, Home and Hobbies, and Personal Care. Scoring is determined by a clinician through a semi-structured and in-depth interview with both the patient and their study partner.

The CDR yields 2 scores, the CDR-G score and the CDR-SB score.

- The **CDR-G** score is calculated using an algorithm and ranges from 0 (no dementia) to 3 (severe dementia).
- The **CDR-SB** scores are calculated by adding the 6 category box scores and range from 0 to 18 (with higher scores indicative of more impairment). This score is used as the primary basis for regulatory review and labeling.

This scale demonstrates acceptable psychometric characteristics (Coley et al. 2011; Cedarbaum et al. 2013) and has been shown to be sensitive enough to detect disease progression, even in populations with less advanced clinical disease (Williams et al. 2013; Wessels et al. 2015).

It is a more commonly used clinical endpoint than iADRS in early stage AD clinical trials and is used as the primary basis for regulatory review and labeling.

ADAS-Cog$_{13}$

The ADAS is a rater-administered instrument that was designed to assess the severity of dysfunction in the cognitive and noncognitive behaviors characteristic of persons with AD (Rosen et al. 1984). The cognitive subscale of the ADAS, the ADAS-Cog$_{13}$, consists of 13 items assessing areas of cognitive function that are the most typically impaired in AD: orientation, verbal memory, language, praxis, delayed free recall, digit cancellation, and maze-completion measures (Mohs et al. 1997). The ADAS-Cog$_{13}$ scale ranges from 0 to 85, with higher scores indicating greater disease severity.

ADCS-ADL

The ADCS-ADL is a 23-item inventory developed as a rater-administered questionnaire that is to be answered by the participant's study partner (Galasko et al. 1997, 2004). The ADCS-iADL subset of Items 6a and 7 to 23 for iADLs was used as a secondary efficacy measure. The focus in the early symptomatic AD population is on the iADLs rather than the basic activities of daily living, which are thought to be affected in more severe stages of the disease. The range for the ADCS-iADL score is 0 to 59, with lower scores indicating greater disease severity.

Time-based clinical endpoints

Time-based endpoints were used to quantify treatment effects based on the clinical scales, because treatment differences, expressed as a point difference on an outcome scale, are difficult to interpret. Time-based endpoints may offer a more understandable way of describing results, especially if treatment is expected to alter the time course of disease (Dickson et al. 2023).

The time-based endpoints that are important for understanding clinical benefit include the following:

Time-based slowing of disease progression

Time-progression model with repeat measures (Raket et al. 2022) of iADRS and CDR-SB was used to estimate time-based slowing of disease progression.

Risk of advancement to next clinical stage and risk of meaningful within-patient change

Another way to contextualize the clinical meaningfulness of these results is to express them by estimating the delay of disease progression.

Clinical staging of disease is assessed by the CDR-Global Score and is described in Figure 1.3. Given the course of disease, irreversible nature of neuronal loss, and the mechanism of action for donanemab targeting removal of amyloid plaques, the primary expectation for amyloid-targeted

agents is to delay disease progression, that is keeping patients at their current, earlier clinical stage of disease longer to preserve meaningful daily functioning longer.

Patients were assessed by the CDR-G score every 3 months for progression to next stage of AD. Advancement to next clinical stage is an event-driven analysis, defined as an increase in the CDR-G score at 2 consecutive visits. For example, patients whose score changed from 0.5 to 1 or greater, or 1 to 2 or greater were considered to have progressed to a worse stage of the disease. These are large clinically meaningful changes for the patient and caregiver.

Within-patient change provides an assessment from the patient's or physician's perspective. Specifically, the MWPC, or minimal clinically important difference, is a threshold over which a patient or physician would consider a given change in score to be meaningful and worthwhile benefit. An MWPC is not the same as a potential treatment effect detected at a study endpoint. The MWPC or minimal clinically important difference for the iADRS and the CDR-SB has previously been established (Andrews et al. 2019; Wessels et al. 2022b; Lansdall et al. 2023).

Stability of clinical symptoms at 1 year

Probability of no change on the CDR-SB at 1 year was assessed. Patients' status was classified as "no progression" if their CDR-SB change from baseline was less than or equal to 0 at 52 weeks.

6.2.1.2.2. Biomarkers

The key biomarker endpoints proposed for labeling include measures that are supportive of the mechanism of action and/or important for dose decision making, namely

- amyloid PET imaging, and
- P-tau217.

Amyloid change from baseline

Reduction of brain amyloid plaque levels is considered a surrogate endpoint reasonably likely to predict clinical benefit. To evaluate the time course and sustainability of the reduction of amyloid plaque levels, the effect of donanemab versus placebo on brain amyloid deposition was assessed as a secondary objective, by measuring the change in brain amyloid plaque deposition via amyloid PET imaging from baseline through Week 76.

Amyloid plaque clearance

Amyloid plaque clearance (defined as amyloid level less than 24.1 CL), as assessed by amyloid PET imaging, was compared in donanemab- and placebo-treated patients for those patients who underwent amyloid PET imaging.

Plasma P-tau217

Plasma P-tau217 is a blood-based biomarker representing downstream AD pathology, associated with both amyloid plaques and tau, and has the highest accuracy in predicting the presence of

AD pathology across plasma biomarkers (Salvadó et al. 2023). A tertiary/exploratory objective was to assess the effect of donanemab versus placebo on P-tau217 change from baseline.

Glial fibrillary acidic protein

Plasma GFAP is a marker of astrocytic activation or proliferation (Escartin et al. 2021). It becomes elevated during cerebral injury or insult, including AD plaque accumulation and neurodegeneration (Price et al. 2021). It is correlated positively with higher amyloid levels (Pereira et al. 2021). Patients with higher GFAP levels show greater clinical decline (Rajan et al. 2020; Pereira et al. 2021). In addition, it is positively associated with tau pathology in subjects with amyloid pathology (Benedet et al. 2021).

6.2.1.2.3. Safety

Safety endpoints

Safety endpoints were assessed in the safety population, which included all randomly assigned patients who received at least 1 dose of double-blind treatment.

Standard safety assessments were

- spontaneously reported AEs
- clinical laboratory tests
- vital sign and body weight measurements
- 12-lead electrocardiograms
- physical and neurological examinations
- MRI (ARIA and emergent radiological findings)
- IRRs, and
- C-SSRS.

Adverse events of special interest

Specific safety topics of interest for this study included, but were not limited to,

- ARIA (including ARIA-E and ARIA-H) and macrohemorrhage, and
- hypersensitivity, immediate and nonimmediate, including IRRs and anaphylaxis.

6.2.1.2.4. Statistical Analyses in Support of Efficacy Measures

Bretz's graphical approach was used to provide strong control of the study-wise type I error rate across the efficacy endpoints in both the low-medium and overall populations. Figure 9.1 presents the graphical testing scheme for Study AACI. Table 6.2 presents the hypotheses included in the graphical testing scheme.

Table 6.2. Hypotheses Included in Graphical Testing Scheme in Study AACI, Low-Medium Tau and/or Overall Populations

	Hypothesis to Test
iADRS	iADRS score change from baseline LS mean differences at Week 76, tested with NCS model with 2 degrees of freedom
CDR-SB	CDR-SB score change from baseline LS mean differences at Week 76, tested with MMRM
ADAS-Cog$_{13}$	ADAS-Cog$_{13}$ score change from baseline LS mean differences at Week 76, tested with NCS model with 2 degrees of freedom
ADCS-iADL	ADCS-iADL score change from baseline LS mean differences at Week 76, tested with NCS model with 2 degrees of freedom
iADRS time-PMRM[a]	Disease progression time saved at Week 76 as measured by the iADRS, tested with time-PMRM model
CDR-SB time-PMRM[a]	Disease progression time saved at Week 76 as measured by CDR-SB, tested with time-PMRM model
CDR-G time-to-event	Difference in hazard of progressing to first meaningful clinical worsening event defined by the CDR-G score, tested with Cox proportional hazard model
CDR-SB no progression[a]	Difference in probability of "no progression" as defined by the CDR-SB at Week 52 (Month 12), tested with GLMM
Amyloid level (CL)	Amyloid level (CL) change from baseline LS mean difference at Week 76, tested with MMRM
Amyloid clearance	Probability of amyloid clearance (<24.1 CL) among donanemab-treated group at Week 24, tested with binomial test
Amyloid clearance	Probability of amyloid clearance (<24.1 CL) among donanemab-treated group at Week 76, tested with binomial test
P-tau217	P-tau217 change from baseline LS mean difference at Week 24, tested with MMRM
P-tau217	P-tau217 change from baseline LS mean difference at Week 76, tested with MMRM
Tau frontal SUVr [a]	Tau PET frontal SUVr change from baseline LS mean difference at Week 76, tested with ANCOVA analysis

Abbreviations: AACI = I5T-MC-AACI; ADAS-Cog$_{13}$ = Alzheimer's Disease Assessment Scale – 13-item Cognitive subscale; ADCS-iADL = Alzheimer's Disease Cooperative Study – instrumental Activities of Daily Living subscale; ANCOVA = analysis of covariance; CDR-G = Clinical Dementia Rating Scale – Global score; CDR-SB = Clinical Dementia Rating Scale – Sum of Boxes; CL = Centiloid; GLMM = generalized linear mixed model; iADRS = integrated Alzheimer's Disease Rating Scale; LS = least squares; MMRM = Mixed Model for Repeated Measures; NCS = natural cubic spline; PET = positron emission tomography; PMRM = progression model with repeat measures; P-tau217 = tau phosphorylated at threonine 217; SUVr = standardized uptake value ratio.

[a] Only the low-medium tau population (not overall population) analysis was included in the graphical testing scheme.

Natural cubic spline

The majority of clinical outcomes were analyzed using NCS with 2 degrees of freedom (Table 6.2). The protocol-specified week value for each participant was utilized as a continuous variable to create NCS basis functions with knot locations: at Week 0, the median observation time, and

Week 76. The model restricted baseline estimates to be the same for treatment and placebo groups. The baseline score and each scheduled postbaseline score were dependent variables in the model. The model's independent variables included NCS basis expansion terms (2 terms), NCS basis expansion term-by-treatment interaction (2 terms), baseline age, concomitant AchEI, and/or memantine use at baseline (yes/no), and randomization stratifying factors: pooled site and baseline tau category (baseline tau category in overall population only). An unstructured variance-covariance matrix was used to model the within-subject errors using restricted maximum likelihood. The Kenward-Roger approximation was used to estimate the denominator degrees of freedom.

Mixed model with repeated measures

The MMRM model was used to assess CDR-SB and amyloid PET (Table 6.2). The analysis model used change from baseline as the dependent variable. The model was adjusted for age, baseline value, visit as a categorical variable, treatment, baseline-by-visit, and treatment-by-visit interactions, AchEI/memantine use at baseline, and randomization stratifying factors: pooled site and for overall population only, baseline tau category.

Time-based analyses

Time-to-clinical worsening and time-progression model with repeat measures (Raket et al. 2022; Dickson et al. 2023) were used to estimate the potential delay of disease progression in donanemab-treated patients compared with the placebo group. A clinical worsening event was defined as meeting a CDR-G score, CDR-SB, and iADRS change from baseline at 2 consecutive visits. A Cox proportional hazard model was fit to estimate the HR of progressing to clinical worsening events between treatment groups.

To further evaluate the treatment benefit of donanemab, patients' status was classified as "nonprogressing" if their CDR-SB change from baseline was less than or equal to 0 at each of the scheduled visits. A generalized linear mixed model was applied to assess the difference in probability of "nonprogressing" by treatment group, and the primary time point for treatment comparison was at Week 52.

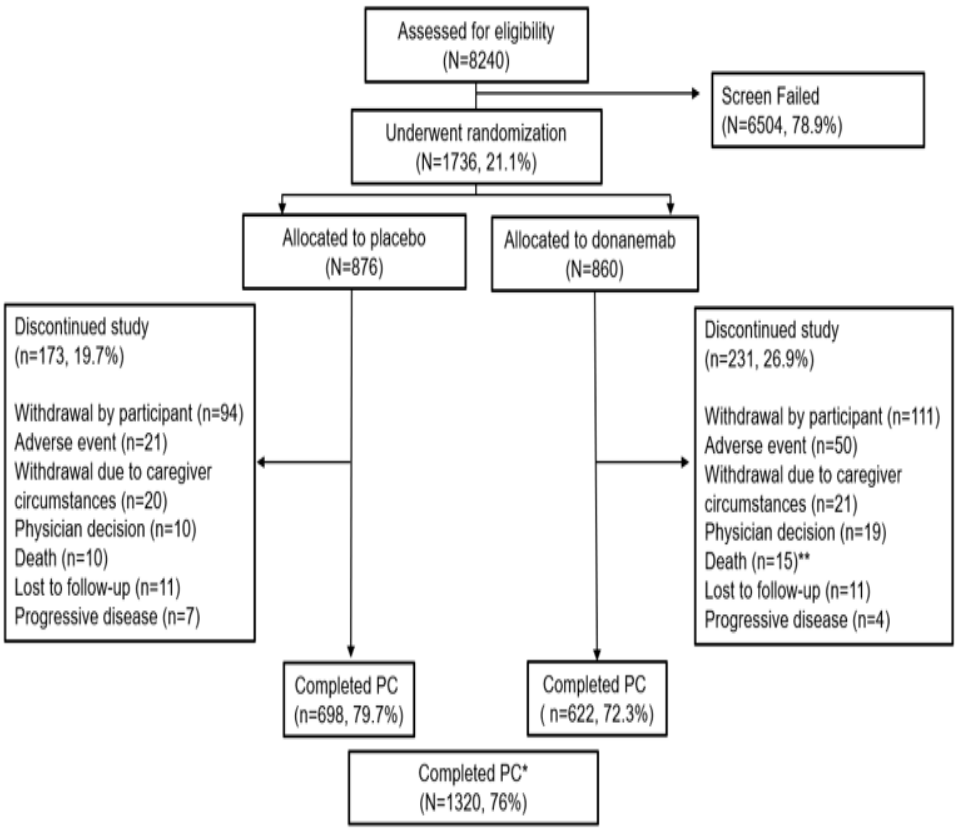
6.2.2. Disposition, Demographics, and Baseline Characteristics

Summary

- Overall, 76% of patients completed the placebo-controlled period of Study AACI.
- Baseline demographic characteristics were similar across donanemab and placebo groups and in both studies, and baseline disease characteristics were reflective of the intended patient population.
- Compared to other contemporary AD clinical trials, the donanemab clinical trials enrolled an older and more clinically advanced population with higher pathological disease burden. These baseline characteristic differences are expected to have resulted in a donanemab population that was both harder to treat and, also, more susceptible to both drug-related ARIA as well as other unrelated AEs or death due to comorbid illness.

6.2.2.1. Patient Disposition

Figure 6.3 shows the patient disposition for the study. A total of 1736 patients were randomly assigned to treatment in the study. The safety population (N = 1727) included all randomly assigned patients who received at least 1 dose of double-blind treatment (donanemab [n = 853] or placebo [n = 874]).



Abbreviations: n = number of patients in the specified category; N = number of patients in the population; PC = placebo controlled.

* Twelve patients did not complete the final visit prior to database lock.

** One additional death occurred in the +57-day follow-up period.

Figure 6.3. Patient disposition for Study AACI.

6.2.2.2. Baseline Demographics and Disease Characteristics

Table 6.3 summarizes baseline demographic and disease characteristics for Study AACI. In general, baseline demographic characteristics were similar across donanemab and placebo groups, and baseline disease characteristics were reflective of the intended patient population.

Study AACI enrolled a population fully characterized by amyloid and tau pathology that included patients with early AD along a spectrum of both pathological and clinical disease, ranging from low-medium to high baseline tau and from MCI to mild dementia patients (consistent with Stage 3 and Stage 4 of AD).

Table 6.3. Demographics and Clinical Characteristics of Patients at Baseline, Study AACI

Demographics	Overall		Low-Medium Tau		High Tau	
	Donanemab (N = 860)	Placebo (N = 876)	Donanemab (N = 588)	Placebo (N = 594)	Donanemab (N = 271)	Placebo (N = 281)
Female sex, n (%)	493 (57.3)	503 (57.4)	325 (55.3)	321 (54.0)	167 (61.6)	181 (64.4)
Mean age, years (SD)	73.0 (6.2)	73.0 (6.2)	74.3 (5.7)	74.3 (5.8)	70.1 (6.2)	70.5 (6.3)
Race, n (%)						
Asian	57 (6.6)	47 (5.4)	48 (8.2)	38 (6.4)	9 (3.3)	9 (3.2)
Black or African American	19 (2.2)	21 (2.4)	17 (2.9)	17 (2.9)	2 (0.7)	4 (1.4)
White	781 (90.9)	807 (92.1)	522 (88.8)	539 (90.7)	258 (95.6)	267 (95.0)
Other[a]	2 (0.2)	1 (0.1)	1 (0.2)	0	1 (0.4)	1 (0.4)
Ethnicity[b] Hispanic/Latino, n (%)	35 (5.7)	36 (5.7)	24 (5.8)	26 (6.3)	11 (5.4)	10 (4.7)
Education, ≥13 years, n (%)	606 (70.5)	637 (72.8)	407 (69.2)	421 (71.0)	198 (73.3)	215 (76.5)
APOE ε4 carrier, n (%)	598 (69.8)	621 (71.2)	421 (71.7)	427 (72.3)	176 (65.4)	193 (68.9)
APOE genotypes, n (%)						
E2/E2	0	1 (0.1)	0	1 (0.2)	0	0
E2/E3	18 (2.1)	20 (2.3)	10 (1.7)	14 (2.4)	8 (3.0)	6 (2.1)
E2/E4	22 (2.6)	25 (2.9)	17 (2.9)	19 (3.2)	5 (1.9)	6 (2.1)
E3/E3	241 (28.1)	230 (26.4)	156 (26.6)	149 (25.2)	85 (31.6)	81 (28.9)
E3/E4	433 (50.5)	450 (51.6)	314 (53.5)	308 (52.1)	118 (43.9)	141 (50.4)
E4/E4	143 (16.7)	146 (16.7)	90 (15.3)	100 (16.9)	53 (19.7)	46 (16.4)
AchEI/memantine use, n (%)	521 (60.6)	538 (61.4)	332 (56.5)	341 (57.4)	188 (69.4)	197 (70.1)
Clinical category by MMSE[e], n (%)						
Mild cognitive impairment (≥27)	146 (17.0)	137 (15.7)	115 (19.6)	116 (19.6)	31 (11.4)	21 (7.5)
Mild AD (20-26)	713 (82.9)	738 (84.3)	472 (80.3)	477 (80.4)	240 (88.6)	260 (92.5)
Moderate AD (<20)	1 (0.1)	0	1 (0.2)	0	0	0
MMSE score[c], mean (SD)	22.4 (3.8)	22.2 (3.9)	23.1 (3.6)	22.8 (3.8)	21.1 (3.9)	20.8 (3.9)
Biomarker measures, mean (SD)						
Amyloid plaque level, in Centiloids[d]	103.5 (34.5)	101.6 (34.5)	102.4 (34.7)	100.9 (35.1)	106.0 (33.8)	103.1 (33.1)
AD signature weighted neocortical flortaucipir SUVr[c,f]	1.34 (0.25)	1.35 (0.26)	1.21 (0.12)	1.21 (0.13)	1.68 (0.17)	1.70 (0.20)
Plasma P-tau217[g], in pg/mL	7.5 (18.5)	6.8 (15.4)	6.6 (17.7)	5.4 (11.3)	9.4 (20.2)	9.9 (21.4)

Abbreviations: AACI = I5T-MC-AACI; AchEI = acetylcholinesterase inhibitor; AD = Alzheimer's disease; APOE ε4= allele subtype 4 of the gene coding for apolipoprotein class E; MMSE = Mini-Mental State Examination; n = number of patients in the specified category; N = number of patients in the population; P-tau217 = tau phosphorylated at threonine 217; SD = standard deviation; SE = standard error; SUVr = standard uptake value ratio.

[a] Includes Multiple and American Indian or Alaskan Native.

[b] Ethnicity reporting was limited to participants in the US and Puerto Rico only.

[c] Last nonmissing MMSE score prior to or at the start of study treatment.

[d] Assessed with florbetapir F 18 or florbetaben F 18 PET.

[e] Based on screening data.

[f] Assessed with flortaucipir F 18 PET. Global tau uptake was measured using a composite neocortical SUVR with white matter signal reference (Southekal et al. 2018).

[g] Plasma P-tau217 denotes plasma-measured phosphorylated tau at threonine 217, a blood biomarker specific to AD and associated with both amyloid and tau pathology (Salvadó et al. 2023).

Note: For all categories, the number of patients with nonmissing data was used as the denominator.

Disease severity at baseline

Study AACI included a broad patient population.

Among randomly assigned patients in Study AACI at screening,

- 16% had clinical disease staging at screening consistent with MCI (MMSE score of at least 27)
- 84% had mild AD (MMSE score of 20 to 26)
- 68% had low-medium tau levels, and
- 32% had high tau levels.

6.2.2.3. Concomitant Medications

Table 6.4 presents the most frequently used concomitant medications (greater than 25% in either group). A total of 1707 patients (98.8%) used a concomitant therapy during Study AACI. Concomitant medication use was generally balanced between donanemab and placebo groups. Concomitant medication use was reported by 847 (99.3%) patients in the donanemab group and by 860 (98.4%) patients in the placebo group. Although certain concomitant medications were taken by slightly more patients in the donanemab or placebo group, these differences did not appear to have an impact on the safety or efficacy outcomes.

Table 6.4. Most Frequently Used Concomitant Medications, Safety Analysis Set, Study AACI

Concomitant Medication, n (%)	Placebo (N = 874)	Donanemab (N = 853)	Total (N = 1727)
Donepezil	429 (49.1)	418 (49.0)	847 (49.0)
COVID-19 vaccine	346 (39.6)	326 (38.2)	672 (38.9)
Acetylsalicylic acid	273 (31.2)	271 (31.8)	544 (31.5)
Cholecalciferol	219 (25.1)	233 (27.3)	452 (26.2)
Atorvastatin	223 (25.5)	223 (26.1)	446 (25.8)
Memantine	231 (26.4)	208 (24.4)	439 (25.4)
Paracetamol	200 (22.9)	225 (26.4)	425 (24.6)

Abbreviations: AACI = I5T-MC-AACI; COVID-19 = coronavirus disease 2019; n = number of patients in the specified category; N = number of patients in the population.

Concomitant antithrombotic use

A total of 711 patients (41.2%) used a concomitant antithrombotic during the study. Antithrombotic use was similar among patients in the donanemab group (n = 348, 40.8%) and placebo group (n = 363, 41.5%). The use of nonaspirin antiplatelets was higher in the donanemab group (n = 52, 6.1%) compared with the placebo group (n = 33, 3.8%). The use of anticoagulants (donanemab group: 9.8%; placebo group: 10.1%) and thrombolytics (donanemab group: 0.1%; placebo group: 0.2%) was similar between donanemab and placebo groups. The most commonly used antithrombotic in both groups was aspirin.

6.2.3. Efficacy Results

Efficacy Summary

Study AACI (TRAILBLAZER-ALZ2) met primary and key secondary clinical efficacy endpoints, in donanemab-treated patients versus placebo-treated patients, with significant differences starting as early as 6 months (all $p<0.05$).

Donanemab-treated patients, in comparison with the placebo-treated patients, showed

- a significant slowing of clinical decline by 22% ($p<0.001$; iADRS) and 29% ($p<0.001$; CDR-SB) in the overall population, and by 35% ($p<0.001$; iADRS) and 36% ($p<0.001$; CDR-SB) in the low-medium tau population, at Week 76
- significant and positive efficacy results across multiple sensitivity and supplementary analyses, supporting robustness of clinical trial outcomes
- a positive clinical efficacy benefit was observed across nearly all subgroups; no findings suggested that any of the subgroups would not benefit from treatment with donanemab, and
- a 37% lower risk of advancement to the next stage of the disease ($p<0.0001$), based on CDR-global score, at Week 76 compared with placebo.

Donanemab is effective irrespective of tau status, with a greater relative benefit for those treated earlier in their course of the disease.

AACI results also marked the first time where a potential disease-modifying drug for AD showed replication of results across 2 different positive studies; AACG and AACI both showed statistically significant and highly similar efficacy.

These clinical efficacy results meet the precedent and regulatory standards for treatment efficacy in AD.

6.2.3.1. Analysis Approach

There were 2 prespecified populations:

- overall, and
- low-medium tau.

The focus of this section is on results in these populations; however, the high-tau population (though not powered) is also presented where appropriate for comparison.

Available biomarker data from the separate Addendum for the no-very low tau population are also presented.

6.2.3.2. Results of Graphical Multiplicity Testing Schema for Primary and Other Endpoints

Table 6.5 provides the results of the graphical multiplicity testing procedure for controlling type I error at 2-sided alpha level of 5%. Donanemab consistently achieved positive results on all the primary and secondary endpoints measuring cognitive and functional decline across both low-medium tau and overall populations.

Table 6.5. Graphical Multiplicity Testing Results, Evaluable Efficacy Set, Study AACI

	Population	Donanemab versus Placebo			
		LS Mean Change Difference (SE), Unless Otherwise Described	% Slowing	Nominal p-Value	Significant versus Placebo?
iADRS NCS2 analyses at Week 76	Overall	2.92 (0.72)	22	<0.001	Yes
	Low-medium	3.25 (0.70)	35	<0.001	Yes
CDR-SB MMRM analyses at Week 76	Overall	-0.70 (0.13)	29	<0.001	Yes
	Low-medium	-0.67 (0.14)	36	<0.001	Yes
ADAS-Cog_{13} NCS2 analyses at Week 76	Overall	-1.33 (0.39)	20	0.0006	Yes
	Low-medium	-1.52 (0.37)	32	<0.001	Yes
ADCS-iADL NCS2 analyses at Week 76	Overall	1.70 (0.44)	28	0.0001	Yes
	Low-medium	1.83 (0.47)	40	<0.001	Yes
iADRS time-PMRM analysis at Week 76	Low-medium	Delayed by 4.4 months	—	<0.001	Yes
CDR-SB time-PMRM analysis at Week 76	Low-medium	Delayed by 7.5 months	—	<0.001	Yes
CDR-G TTE analyses	Overall	HR is 0.63	—	<0.0001	Yes
	Low-medium	HR is 0.61	—	<0.001	Yes
CDR-SB no progressor analysis at Week 52	Low-medium	Probability of DPF is 0.47 (placebo is 0.29)	—	<0.00001	Yes
Amyloid Centiloid change from baseline at Week 76	Overall	-86.4 (1.3)	—	<0.0001	Yes
	Low-medium	-88.2 (1.5)	—	<0.0001	Yes
Amyloid clearance at Week 24	Overall	29.7% amyloid negative (placebo is 0.2%)	—	<0.0001	Yes
	Low-medium	34.2% amyloid negative (placebo is 0.2%)	—	<0.0001	Yes

	Population	Donanemab versus Placebo			
		LS Mean Change Difference (SE), Unless Otherwise Described	% Slowing	Nominal p-Value	Significant versus Placebo?
Amyloid clearance at Week 76	Overall	76.4% amyloid negative (placebo is 0.3%)	—	<0.0001	Yes
	Low-medium	80.1% amyloid negative (placebo is 0%)	—	<0.0001	Yes
P-tau217 change from baseline to Week 24	Overall	-0.16 (0.01)	—	<0.0001	Yes
	Low-medium	-0.19 (0.01)	—	<0.0001	Yes
P-tau217 change from baseline to Week 76	Overall	-0.22 (0.01)	—	<0.0001	Yes
	Low-medium	-0.25 (0.01)	—	<0.0001	Yes
Tau frontal SUVr change from baseline to Week 76	Low-medium	0.0002	—	0.9684	No

Abbreviations: AACI = placebo-controlled period of Study AACI; ADAS-Cog$_{13}$ = Alzheimer's Disease Assessment Scale – 13-item Cognitive subscale; ADCS-iADL = Alzheimer's Disease Cooperative Study – instrumental Activities of Daily Living subscale; CDR-G = Clinical Dementia Rating Scale – Global Score; CDR-SB = Clinical Dementia Rating Scale – Sum of Boxes; DPF = disease progression free; HR = hazard ratio; iADRS = integrated Alzheimer's Disease Rating Scale; LS = least squares; PMRM = progression model for repeat measures; NCS2 = natural cubic spline model with 2 degrees of freedom; MMRM = Mixed Model for Repeated Measures; P-tau217 = tau phosphorylated at threonine 217; SE = standard error; SUVr = standard uptake value ratio; TTE = time to event.

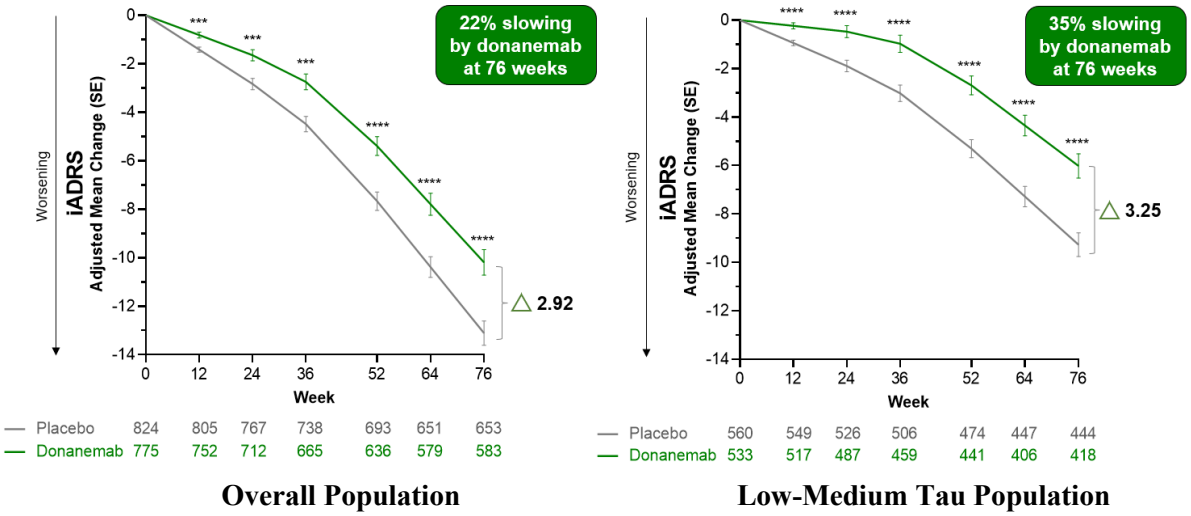
6.2.3.3. Clinical Results

All clinical endpoints of cognitive and functional decline were met and showed highly statistically significant clinical benefits with similar magnitude. Efficacy was consistent across subgroups for primary and key secondary clinical measures and was further supported by biomarkers relevant to disease modification.

6.2.3.3.1. iADRS

Study AACI met its primary objective in demonstrating a significant slowing of clinical progression relative to placebo.

At Week 76, donanemab-treated patients had a significant slowing of clinical progression relative to placebo by 22% in the overall population ($p<0.0001$) and by 35% in the low-medium tau population ($p<0.0001$), as measured by the primary outcome of iADRS change from baseline (Figure 6.4).

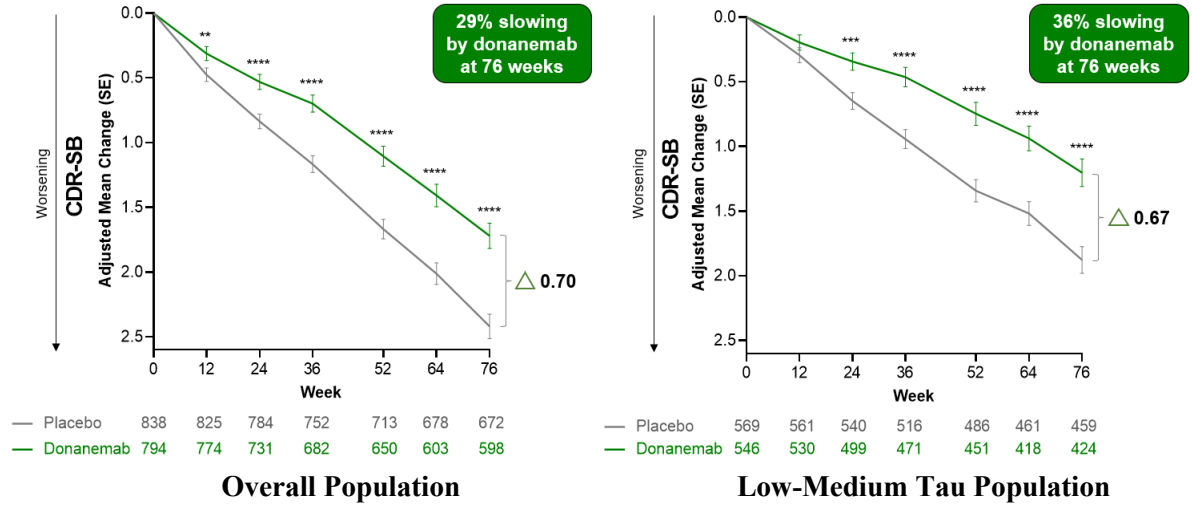


Abbreviations: AACI = I5T-MC-AACI; iADRS = integrated Alzheimer's Disease Rating Scale; NCS = natural cubic spline; SE = standard error.
Note: *** p<0.001, **** p<0.0001.

Figure 6.4. NCS2 analysis of iADRS at Week 76, Study AACI.

6.2.3.3.2. CDR-SB

At Week 76, donanemab-treated patients had a significant slowing of clinical progression relative to placebo by 29% in the overall population (p<0.0001) and by 36% in the low-medium tau population (p<0.0001), as measured by CDR-SB change from baseline (Figure 6.5).



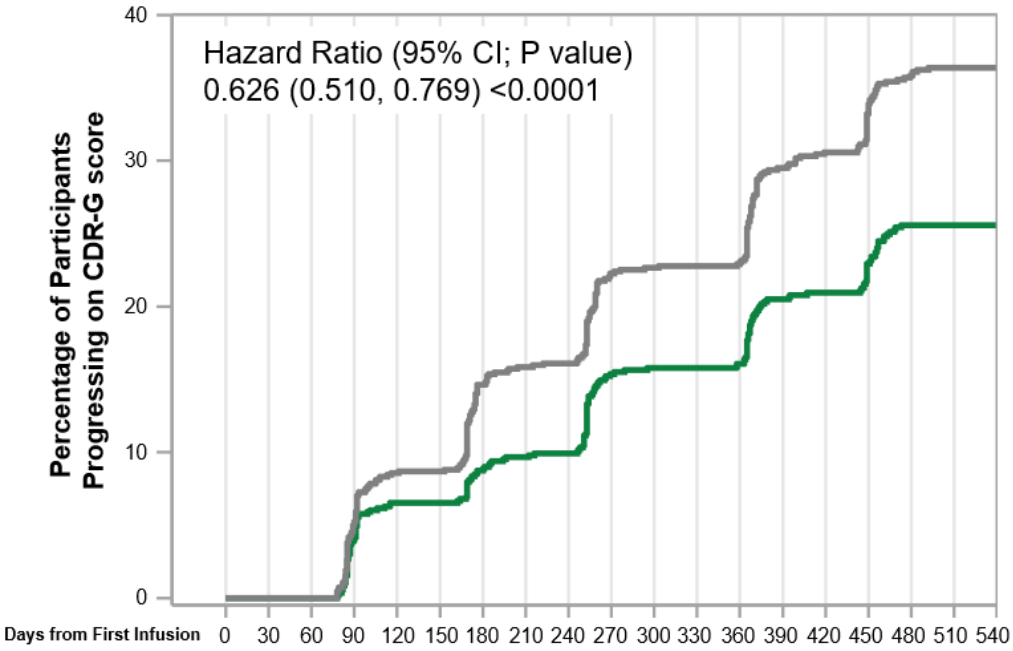
Abbreviations: AACI = I5T-MC-AACI; CDR-SB = Clinical Dementia Rating Scale – Sum of Boxes; MMRM = Mixed Model for Repeated Measures; SE = standard error.
Note: ** p<0.01, *** p<0.001, **** p<0.0001.

Figure 6.5. MMRM analysis of CDR-SB at Week 76, Study AACI.

6.2.3.3.3. Clinically Meaningful Benefit of Slowing Progression to the Next Clinical Stage

CDR-G: risk of progression to the next stage of disease

In addition to slowing disease progression, donanemab treatment also delayed advancement to the next stage of disease. Compared with placebo-treated patients, donanemab-treated patients in the overall population had a 37% lower risk of progressing to the next stage of disease as measured by the CDR-G score (HR: 0.63; 95% CI: 0.51, 0.77; p<0.0001) through Week 76 (Figure 6.6). At Week 76, donanemab-treated patients showed 39% lower risk of time progression to a later stage of disease as measured by CDR-G score (HR: 0.61; p<0.001) in the low-medium tau population.



Abbreviations: AACI = I5T-MC-AACI; CDR-G = Clinical Dementia Rating Scale – Global score; CI = confidence interval; n = number of patients in the specific category; N = number of patients; SE = standard error.

Note: Gray line indicates the placebo group, and green line indicates the donanemab group. Hazard ratio and p-value were generated using a Cox proportional hazards model adjusted for baseline age, baseline value, and baseline acetylcholinesterase inhibitor/memantine use, and stratified by pooled investigator.

Figure 6.6. Risk of progression: CDR-Global Score (Overall Population), Study AACI.

CDR-SB: time-based slowing of disease progression

At Week 76, donanemab treatment significantly delayed disease progression, as measured by CDR-SB, by 5.4 months in the overall population and 7.5 months in the low-medium tau population (Table 6.6).

Table 6.6. Time-Saved Progression Model for Repeated Measures, CDR-SB at Week 76, Study AACI

Time-PMRM	Overall	Low-Medium Tau
Time saved[a] (95% CI)	5.44 (3.9, 6.98)	7.53 (5.69, 9.36)
p-value	<0.001	<0.001
% time slowing	31	42.9

Abbreviations: AACI = I5T-MC-AACI; CDR-SB = Clinical Dementia Rating Scale – Sum of Boxes; CI = confidence interval; PMRM = progression model for repeated measures.

[a] Time saved in months.

Note: Results based on Time-PMRM model with proportionality assumption.

CDR-SB: risk of meaningful within-patient change

Compared with placebo-treated patients, donanemab-treated patients had a lower risk of experiencing a MWPC, as measured by CDR-SB:

- 38% (HR: 0.62; nominal p<0.001) lower risk of MWPC in the overall population, and
- 40% (HR: 0.60; nominal p<0.001) lower risk of MWPC in the low-medium tau population.

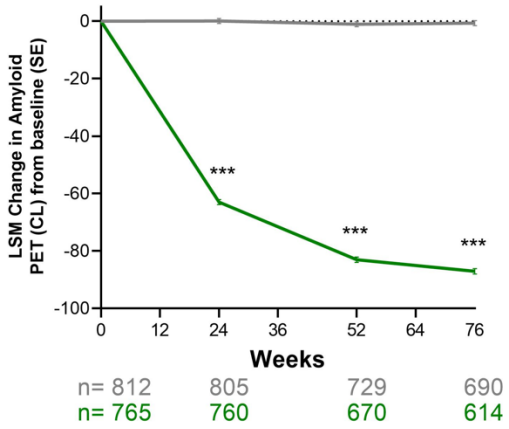
CDR-SB: stability of clinical symptoms at 1 year

Compared with placebo-treated patients, more donanemab-treated patients remained stable in their disease showing **no** decline in CDR-SB at Week 52:

- 36% donanemab-treated patients were stable versus 23% placebo-treated patients in the overall population (p<0.00001), and
- 47% donanemab-treated patients were stable versus 29% placebo-treated patients in the low-medium tau population (p<0.00001).

6.2.3.3.4. Amyloid PET

Compared with placebo-treated patients, donanemab-treated patients had statistically significantly more brain amyloid plaque reduction, as assessed by the amyloid PET measurement, in the overall population (LS mean change ± SE: -86.4 ± 1.3 CL units, p<0.0001) and in the low-medium tau population (LS mean change ± SE: -88.2 ± 1.5 CL units, p<0.0001) at Week 76 (Figure 6.7).



Abbreviations: AACI = placebo-controlled period of Study AACI; CL = Centiloid; LSM = least squares mean; MMRM = Mixed Model for Repeated Measures; n = number of patients in the specified category; SE = standard error. Note: *** p<0.0001.

Figure 6.7. MMRM analysis of change in amyloid level (Centiloid units, CL) from baseline to Week 76, Study AACI (Overall Population).

6.2.3.3.5. Sensitivity and Supplementary Analyses

Multiple sensitivity and supplementary analyses support the robustness of the primary efficacy results, demonstrating generally consistent results across various models and assumptions (iADRS and CDR-SB; Table 6.7). Preplanned efficacy analyses were conducted using evaluable efficacy set (that is, modified intent-to-treat) population, and missing data were handled by mixed model with data missing at random assumption. Missingness has been robustly explored in sensitivity analyses, with multiple imputation, and such analyses support the robustness of the prespecified method and outcomes.

Tipping point analyses were conducted to assess the data missing at random assumption. In this analysis, an artificial worsening value was added to the imputed values (based on missing at random assumption) for the dropouts from donanemab group, and the added value was increased in each round of analysis until the treatment difference was no longer statistically significant. The analysis on iADRS showed that decline in donanemab-treated dropouts would need to be 5 points or more (for both overall and low-medium tau populations) than those who remained in the study to overturn the statistical significance of primary analyses.

In addition, supplementary analyses based on intent-to-treat population were conducted, which included missing values multiply imputed with missing at random and missing not at random assumptions each. Multiple imputation with missing not at random included copy increment from reference, which assumed that postdiscontinuation donanemab-treated dropouts would progress similar to the placebo-treated patients, and some more conservative approaches such as Jump to Reference imputation for all dropouts but special treatment for dropouts due to ARIA/death, including imputing their postdropout values from the fastest 20% progressors, or as the worst observed change values from the corresponding visits. All these analyses consistently

showed the benefits of donanemab treatment and confirmed the robustness of findings from primary efficacy analyses.

Table 6.7. Change in Baseline in iADRS or CDR-SB Score at Week 76 Sensitivity and Supplementary Analysis, Study AACI

Type of Sensitivity or Supplementary Analysis	Analysis Set	Week 76, Dona vs PBO p-Value	
		Overall	Low-Medium Tau
iADRS[a]			
Censored data after first occurrence of ARIA-E or IRR	EES	0.011	<0.001
Model included 2 levels for donanemab: with and without ARIA-E during the study	EES, Dona with ARIA-E	<0.001	0.001
	EES, Dona without ARIA-E	0.004	<0.001
Imputed worst response for deaths at all visits following death	EES	0.001	0.001
Per-protocol analysis	Per-Protocol Set	<0.001	<0.001
Completer analysis	Completers Set	<0.001	<0.001
Multiple imputation with MAR: imputation process included indicators of treatment discontinuation and ARIA occurrence	ITT	<0.0001	<0.0001
Multiple imputation with MNAR: imputed values using CIR method	ITT	0.0007	<0.0001
Multiple imputation with MNAR: imputed values from worst 20% responders for dropouts due to death and ARIA, and imputed values using Jump to Reference method for other missing data	ITT	0.0361	0.0018
Multiple imputation with MNAR: imputed values as worst observed change for dropouts due to deaths and ARIA, and imputed values using Jump to Reference for other missing data	ITT	0.1869	0.0862
CDR-SB[b]			
Model included 2 levels for donanemab: with and without ARIA-E during the study	EES, Dona with ARIA-E	<0.001	<0.001
	EES, Dona without ARIA-E	<0.001	<0.001
Multiple imputation with MAR: imputation process included indicators of treatment discontinuation and ARIA occurrence	ITT	<0.0001	<0.0001
Multiple imputation with MNAR: imputed values using CIR method	ITT	<0.0001	<0.0001

Type of Sensitivity or Supplementary Analysis	Analysis Set	Week 76, Dona vs PBO p-Value	
		Overall	Low-Medium Tau
Multiple imputation with MNAR: imputed values from lowest 20% responders for dropouts due to death and ARIA, and imputed values using Jump to Reference method for other missing data	ITT	0.0001	0.0003
Multiple imputation with MNAR: imputed values as worst observed change for dropouts due to deaths and ARIA, and imputed values using Jump to Reference method for other missing data	ITT	0.0091	0.0190

Abbreviations: AACI = I5T-MC-AACI; ARIA = amyloid-related imaging abnormalities; ARIA-E = amyloid-related imaging abnormalities–edema/effusions; CDR-SB = Clinical Dementia Rating Scale – Sum of Boxes; CIR = copy increment from reference; EES = evaluable efficacy set; iADRS = integrated Alzheimer's Disease Rating Scale; IRR = infusion-related reaction; ITT = intent to treat; MAR = missing at random assumption; MMRM = Mixed Model Repeated Measures; MNAR = missing not at random assumption; NCS = natural cubic spline; PBO = placebo.

[a] NCS2 analysis.

[b] MMRM analysis.

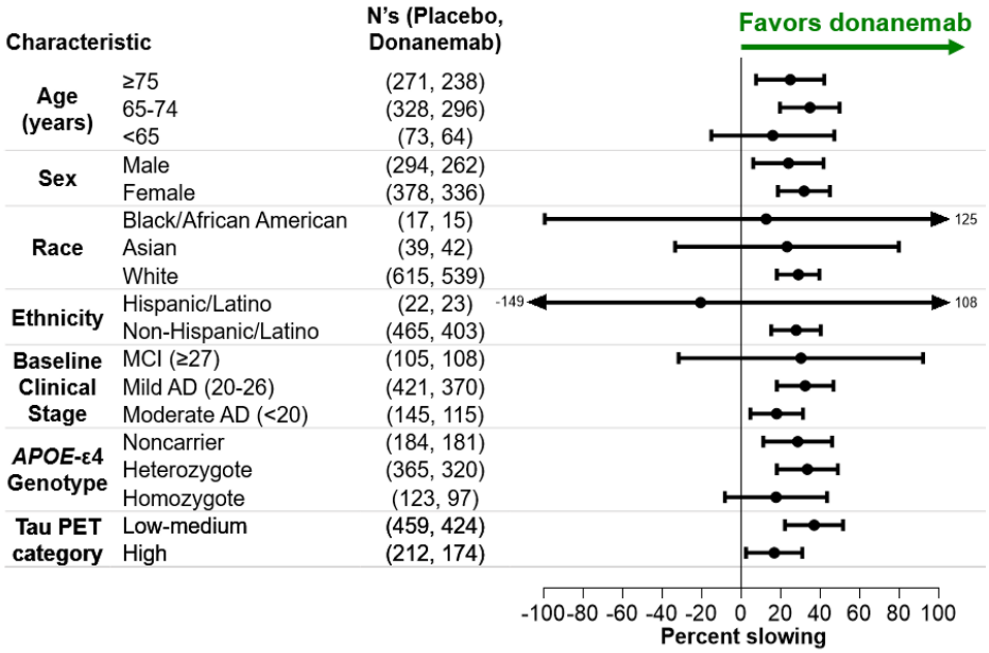
6.2.3.3.6. Efficacy across Subgroups

Treatment effects were further assessed in subgroups and subpopulations of interest, defined by screening or baseline characteristics, including demographics, APOE ε4 status, concomitant medications, clinical staging, and brain tau burden. Various statistical models and assumptions were used. Analyses for CDR-SB are presented here in Figure 6.8.

Consistently, efficacy benefit favored donanemab treatment across clinical outcomes in nearly all the subgroups examined. The benefits were evident including in patients with high tau and patients with APOE ε4 homozygotes. Though none of these subgroup analyses were powered for statistical confirmation, the results suggest a generalizability of donanemab efficacy across populations. In the 2 smallest subgroups, Black/African American race subgroup and Hispanic/Latino ethnicity subgroup, the point estimate of mean treatment effect for 1 outcome measure did not favor donanemab but was also inconsistent across clinical outcomes with wide CIs. All subpopulations are expected to have the potential to benefit from donanemab treatment.

Clinical efficacy benefits based on tau levels

Table 6.8 presents an overall summary of key clinical endpoint results in the prespecified overall and low-medium tau populations, and the high-tau subpopulation.



Abbreviations: AACI = I5T-MC-AACI; AD = Alzheimer's disease; APOE = gene coding for apolipoprotein class E; CDR-SB = Clinical Dementia Rating Scale – Sum of Boxes; MCI = mild cognitive impairment; N = number of patients; PET = positron emission tomography.

Figure 6.8. CDR-SB: subgroup analyses (Overall Population), Study AACI.

Table 6.8. Key Clinical Endpoints across Tau Groups, Study AACI

	Overall		Low-Medium Tau		High Tau[a]	
	Placebo N = 876	Donanemab N = 860	Placebo N = 594	Donanemab N = 588	Placebo N = 281	Donanemab N = 271
CDR-SB[b]						
Mean baseline	3.89	3.92	3.64	3.72	4.43	4.36
Change from baseline	2.42	1.72	1.88	1.20	3.34	2.64
Difference from placebo (%)	–	-0.70 (29%) p<0.001	–	-0.67 (36%) p<0.001	–	-0.69 (21%) p = 0.006
ADAS-Cog$_{13}$[c]						
Mean baseline	29.16	28.53	27.60	27.41	32.42	31.02
Change from baseline	6.79	5.46	4.69	3.17	11.08	10.57
Difference from placebo (%)	–	-1.33 (20%) p<0.001	–	-1.52 (32%) p<0.001	–	-0.51 (5%) p = 0.531
ADCS-iADL[c]						
Mean baseline	47.98	47.96	48.56	48.20	46.71	47.42
Change from baseline	-6.13	-4.42	-4.59	-2.76	-9.25	-8.24
Difference from placebo (%)	–	1.70 (28%) p<0.001	–	1.83 (40%) p<0.001	–	1.01 (11%) p = 0.264

Abbreviations: AACI = I5T-MC-AACI; ADAS-Cog$_{13}$ = Alzheimer's Disease Assessment Scale – 13-item Cognitive Subscale; ADCS-iADL = Alzheimer's Disease Cooperative Study – instrumental Activities of Daily Living subscale; CDR-SB = Clinical Dementia Rating – Sum of Boxes; MMRM = Mixed Model for Repeated Measures; N = number of patients in the population; NCS2 = natural cubic spline with 2 degrees of freedom.

[a] High tau was a small subpopulation that was not statistically powered in Study AACI.

[b] MMRM analysis.

[c] NCS2 analysis.

Note: Overall population consisted of patients with low-medium tau or high tau at baseline.

Similarly, when evaluating the risk for individuals to progress as measured by the CDR-G score, almost identical reductions were observed for the low-medium and high tau subgroups (39% [HR 0.61] and 38% [HR 0.62] reduction of risk of advancing to the next stage of disease at 18 months, respectively) (Table 6.9). This benefit was observed despite the more aggressive disease and more rapid rate of progression for the high tau subgroup, thereby highlighting that there is a clinically meaningful impact at the patient level.

Note that Study AACI (with 100% tau imaging) was not powered to precisely estimate the effect size specifically within the smaller-sized high tau subgroup, and thus no formal statistical efficacy comparisons can be made between the low-medium and high tau populations.

Table 6.9. Benefits of Donanemab across Tau Populations Based on Change in CDR-G Time-to-Event Analysis (MCID), Study AACI

Events	Overall	Low-Medium Tau	High Tau
	Dona (N = 805) vs PBO (N = 844)	Dona (N = 555) vs PBO (N = 573)	Dona (N = 258) vs PBO (N = 275)
Reduced risk of advancing to the next stage of disease at 18 months	37% (p<0.0001)	39% (p<0.001)	38% (p = 0.004)

Abbreviations: AACI = I5T-MC-AACI; AD = Alzheimer's disease; CDR-G = Clinical Dementia Rating-Global Score; MCID = minimal clinically important difference; N = number of patients; PBO = placebo.

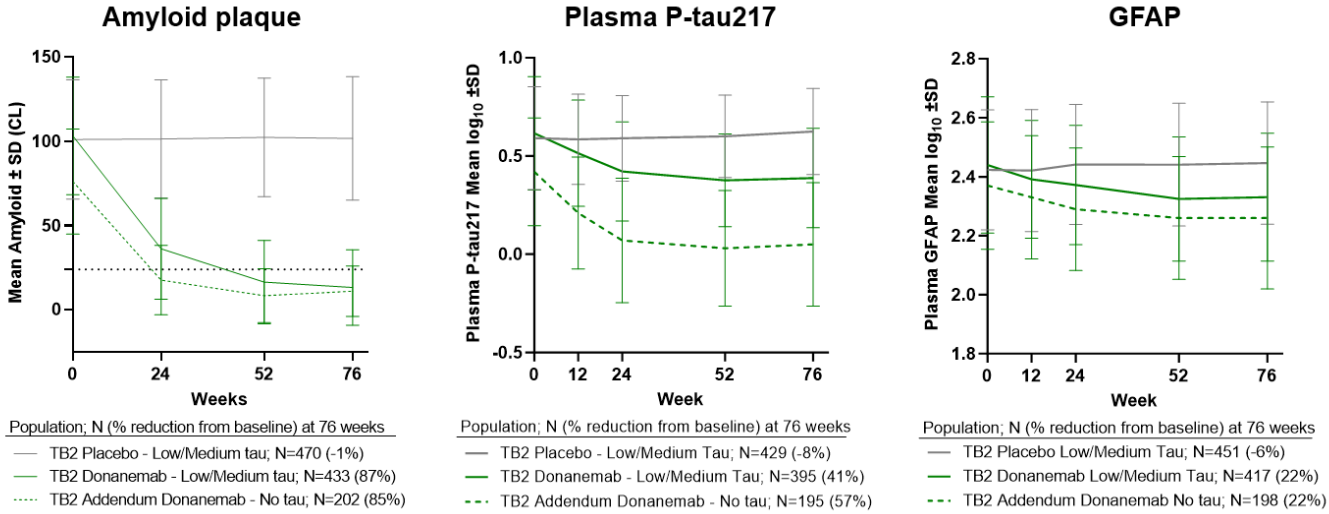
Efficacy in the no-very low tau population (separate Addendum)

Patients with no-very low tau pathology were excluded from AACI because their early disease stage would not be predicted to progress meaningfully over the constrained 18-month study duration, thereby limiting the ability to show a clinical benefit versus placebo. To demonstrate the safety and key disease related biomarker changes within this subgroup, Lilly also conducted a separate addendum to AACI that enrolled patients (n = 1053) solely based on confirmation of amyloid pathology, inclusive of patients known to be no-very low tau. Note that the no-very low tau pathology group (n=250) enrolled in this addendum represents the largest to-date characterization of this population treated with an amyloid-targeting therapy.

Biomarker efficacy for no-very low tau

Biomarkers measured in the no-very low tau population included treatment-related amyloid clearance, P-tau217 and GFAP. There were positive treatment responses for these biomarkers in the no-very low tau population relative to other tau groups (Figure 6.9). In general, the no-very low tau group has lower baseline values for all biomarkers, consistent with earlier disease stage, and demonstrates equally robust response to amyloid lowering. In addition, 89% of patients with no-very low tau achieve amyloid clearance (less than 24.1 CL) by 1 year of treatment.

These results are consistent with the data presented at the recent Clinical Trials Alzheimer's Disease 2023 conference. Lilly's modeling data suggest greater clinical benefit can occur in patients with the earliest disease pathology, and patients with less baseline tau levels have greater relative treatment response on both the iADRS and CDR-SB scales (Mintun et al. 2023). These results further support the rationale for evaluating the efficacy of donanemab in a preclinical AD population (that is, patients with amyloid pathology but asymptomatic).



Abbreviations: AACI = I5T-MC-AACI; CL = Centiloid; GFAP = glial fibrillary acidic protein; N = number of patients; TB2 = TRAILBLAZER-ALZ 2; SD = standard deviation.
Amyloid plaque panel: Dotted line = 24.1 CL threshold for amyloid-positive status.
"No tau" refers to the no-very low tau population (insufficient tau for Study AACI placebo-controlled period inclusion).

Figure 6.9. Donanemab-mediated biomarker responses in patients with no-very low tau, (Study AACI and AACI Addendum).

Efficacy across tau levels conclusion

Donanemab is an amyloid-targeting therapy that specifically binds to and removes insoluble amyloid plaques. Robust amyloid plaque removal by donanemab has been demonstrated across clinical trials and irrespective of baseline tau levels. Furthermore, the clinical efficacy data from the overall treatment population confirm that efficacy benefit can be achieved in patients with early symptomatic AD irrespective of tau pathology. Clinical efficacy results in the overall population support that testing for tau pathology is not required in clinical practice.

Collectively, these findings support the use of donanemab in all patients with early symptomatic AD (that is, patients with MCI or mild dementia) and that confirmed amyloid pathology is sufficient biomarker evidence for treatment eligibility.

6.2.3.4. Efficacy Results in Support of Limited-Duration Dosing Option

Donanemab specifically binds to and removes brain amyloid plaques. The donanemab clinical program was designed to allow patients to complete their course of treatment based on observed amyloid-imaging results, demonstrating removal of brain amyloid plaque. Limited-duration dosing is supported by

- Almost half of the patients achieved treatment-related amyloid clearance by Week 52 (Section 6.2.3.4.1)

- Following treatment completion, there was a slow reaccumulation rate of 2.8 Centiloids (CL) per year (Figure 5.1) and no rebound of amyloid plaque in the 12 months following treatment completion at 6 months (Figure 6.10).
- Notably, significant efficacy was observed at 18 months among patients that achieved early treatment-related amyloid clearance (that is, the collective group of patients eligible to move to placebo at either 6 months or 12 months) with continued widening of drug effect even after treatment has been stopped (demonstrated by the numerically increasing difference between donanemab and placebo of CDR-SB among the patients that switched to placebo at 52, 64, and 72 weeks; Figure 1.5).

Collectively based on this clinical trial design and these results, clinicians and patients should have the option to consider stopping treatment once treatment-related amyloid clearance is achieved.

6.2.3.4.1. Amyloid Clearance

In Phase 3 Study AACI, patients were eligible for a reduction to placebo based on predefined amyloid-imaging criteria at Weeks 24, 52, and 76 (Table 6.10). The majority of donanemab-treated patients in the overall population completed their course of treatment by Week 76 as a result of meeting the prespecified amyloid-imaging criteria for amyloid plaque clearance.

Table 6.10. Percentage of Donanemab-Treated Patients Who Met the Reduction to Placebo Criteria Based on Amyloid PET, Study AACI

	Week 24	Week 52	Week 76
Overall Population, % (n/N)	17.1 (130/761)	46.6 (313/672)	69.2 (429/620)

Abbreviations: AACI = I5T-MC-AACI; CL = Centiloid; n = number of patients in the specified category; N = number of patients in the population; PET = positron emission tomography.

Notes: Included patients from unscheduled visits at each time point. Reduction to placebo criteria was defined as amyloid plaque levels less than 11 CL at 1 visit, or less than 25 CL at 2 consecutive visits, on amyloid PET scan.

In a real-world setting, treatment could be stopped once a patient achieves “treatment-related amyloid clearance”. This is defined as amyloid plaque levels less than 24.1 CL, a level thought to be pathological for AD. This level of amyloid plaque clearance is also consistent with a negative visual read on an amyloid PET scan. In Study AACI, over three-fourths of donanemab-treated patients in the overall population achieved treatment-related amyloid clearance by Week 76 (Table 6.11).

Table 6.11. Percentage of Donanemab-Treated Patients That Achieved Treatment-Related Amyloid Clearance, Study AACI

	Week 24	Week 52	Week 76
Overall Population, % (n/N)	29.7 (226/761)	66.1 (443/670)	76.4 (469/614)

Abbreviations: AACI = I5T-MC-AACI; CL = Centiloid; n = number of patients in the specified category; N = number of patients in the population; PET = positron emission tomography.

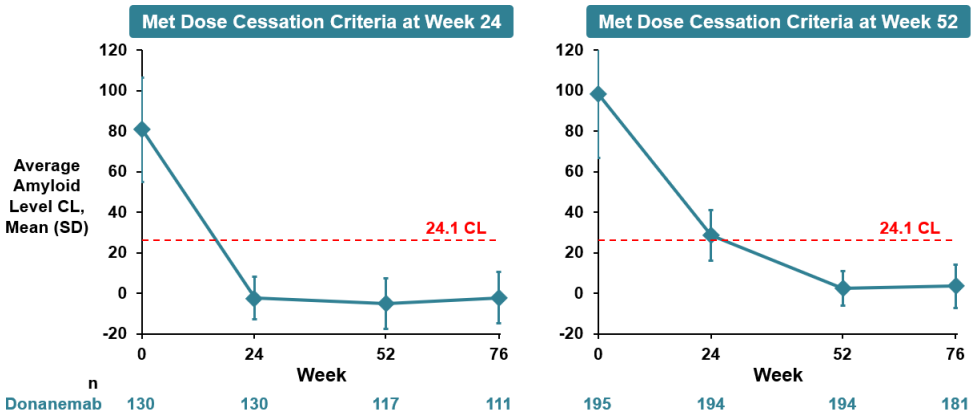
Note: Treatment-related amyloid clearance was defined as amyloid plaque levels less than 24.1 CL on amyloid PET scan, which is consistent with a negative visual read.

6.2.3.4.2. Efficacy Results in Patients Who Stopped Treatment Based on Amyloid Clearance

Patients in the overall population who achieved predefined amyloid clearance levels at either Week 24 or Week 52 continued to show separation from placebo in CDR-SB change from baseline at Week 76 (demonstrated by the numerically increasing difference between donanemab and placebo of CDR-SB among the patients that switched to placebo at 52, 64, and 72 weeks; Figure 1.5). These results support that efficacy benefit continues to widen after amyloid plaque is considered to be cleared and dosing has been stopped.

6.2.3.4.3. Amyloid Plaque Trajectory Once Cleared

Study AACI allowed cessation of dosing for donanemab-treated patients when amyloid plaque was cleared based on amyloid imaging. Treatment was completed (dosing stopped) when either the participant showed amyloid clearance below 11 CL at a single visit (that is, as early as 24 weeks) or below 25 CL at 2 consecutive visits (that is, as early as 52 weeks). Additional PET scans were collected after dose cessation. No significant amyloid plaque increases were observed in the 12 months following treatment completion at 6 months (Figure 6.10).



Abbreviations: CL = Centiloid; SD = standard deviation.

Figure 6.10. Amyloid levels remain low after treatment-related amyloid clearance in donanemab group (Overall Population).

PD of amyloid (Section 5.2) suggest that the overall reaccumulation rate of amyloid plaque is similar to the natural accumulation rate and is approximately 3 CL per year. Therefore, it is likely to take several years for amyloid plaque to return to pathologic levels (that is, above 24.1 CL) once it is considered cleared.

Real-world application

Lilly has received consistent feedback from patients, caregivers, and healthcare professionals that this approach has the potential to decrease treatment burden, an important consideration for this vulnerable and elderly population. Payers, including the Centers of Medicare and Medicaid Services (CMS), have also expressed a great deal of interest in the potential for limited-duration dosing, as this may significantly lower the cost of care in comparison to chronically dosed medications. This approach also aligns with our mechanistic understanding of donanemab – primarily that once the target is cleared from the brain, continued dosing of donanemab is likely not beneficial and only adds to treatment burden and potential risks.

Lilly acknowledges that the decision to implement this limited treatment approach will be individualized in clinical practice and has recommended labeling that would provide flexibility to prescribing decisions. Of note, CMS recently implemented coverage policy changes that eliminate the limit on the number of amyloid PET scans per patient, allowing patients to access additional amyloid PET scans to evaluate for treatment response if desired.

Lilly expects physicians to use clinical judgment and take individualized patient information into account when assessing dosing duration and timing of amyloid measurement, as they gain more experience in prescribing donanemab over time. In a real-world or clinical practice setting, this would include assessing response to treatment, duration of treatment, and whether the patient has achieved a sufficient reduction in amyloid plaque. The assessment of reduction in amyloid plaque would likely be driven by a negative visual amyloid PET scan, measured by less complex methods than the study-defined rules in Study AACI. A negative visual amyloid PET scan is consistent with a quantitative value of less than 24.1 CL (Wang et al. 2024). Using this approach, it is estimated that approximately 70% of donanemab-treated patients would achieve treatment-related amyloid clearance at the end of a 1-year treatment regimen. As noted in the proposed labeling, it is up to the clinician to determine whether to stop treatment with donanemab when amyloid plaque is considered cleared.

6.2.4. Safety Results

Safety Summary

Donanemab has a safety profile consisting of known class risks.

The safety findings are similar across the different safety analysis datasets, regardless of analysis approach, and generally consistent with the emerging understanding of the safety profile for amyloid-targeting antibody therapies.

A similar frequency of SAEs and TEAEs was reported for the placebo and donanemab treatment groups. There were more discontinuations from study treatment and from study in the donanemab group, most due to IRRs or ARIA.

Consistent with the class of amyloid-targeting therapies, common AEs identified as ADRs for labeling include ARIA-E, ARIA-H, IRRs, and headache. Although less frequently reported, anaphylactic reaction (0.3%) has also been included as an ADR of donanemab treatment in labeling.

In the pre-specified integrated safety analysis in Dona-PC, which accounted for adverse events leading to death occurring within the placebo-controlled period, there were 18 (1.8%) deaths reported for donanemab-treated patients and 12 (1.2%) for placebo. Except for 3 deaths associated with ARIA, no pattern or trend was reported in the type of event, timing, frequency, or nature of the events that led to death. Most were a single type of event, each presenting with multiple risk factors. The causes of death were primarily explained by patient age, disease progression, comorbidities in patient medical history, and/or the use of confounding concomitant medications.

Using an updated methodology that considered any death occurring from first dose to 76 weeks of treatment irrespective of whether the patient was still on active treatment or had withdrawn from the study and incorporating all known vital status information as of 9 May 2024, there were 20 (2.0%) deaths reported for donanemab-treated patients and 17 (1.7%) for placebo. Aside from the 3 ARIA-related deaths, there were 17 (1.7%) non-ARIA related deaths reported for donanemab-treated patients and 17 (1.7%) for placebo. Additional mortality analyses conducted to further clarify the risk of mortality across treatment groups demonstrated similar findings and conclusions. Beyond the known class-risk of ARIA with a low frequency of fatal events (0.3%), there is no evidence of an increase in risk of mortality or excess death related to donanemab treatment.

Overall, ARIA-E was observed in 24% and ARIA-H in 31% of donanemab-treated patients in the Dona-PC analysis set. The majority of these were mild to moderate in radiographic severity, nonserious and asymptomatic. Symptomatic ARIA-E occurred in 6% and symptomatic ARIA-H occurred in 1% of patients treated with donanemab. Total serious ARIA-E or ARIA-H was 2%. Serious ARIA-E (for example, requiring hospitalization) was observed in 1.5% of patients and serious ARIA-H was observed in 0.4% of patients. Clinical symptoms associated with symptomatic and serious ARIA often included headache and confusion, with dizziness, nausea, and seizure reported less frequently. Deaths associated with ARIA were uncommonly observed with a total of 3 deaths in the placebo-controlled integrated safety data.

Most ARIA occurred by the sixth infusion or 24 weeks with most serious ARIA occurring by the third infusion or in the first 12 weeks. Median time to radiographic resolution for ARIA-E was 59 days (approximately 8 weeks).

Risk factors for ARIA included APOE e4 carrier status with homozygotes exhibiting a higher frequency than heterozygotes, and heterozygotes greater than noncarriers. Other key risk factors for ARIA were identified from baseline MRI findings and include superficial siderosis and the number of microhemorrhages.

Intracerebral hemorrhage greater than 1 cm was uncommonly reported in donanemab-treated patients (0.3%) and placebo-treated patients (0.2%).

IRRs were commonly observed (8.5%). Anaphylaxis was uncommonly observed (0.3%). Most of the IRRs were mild or moderate in severity (94%), occurred during the infusion or within 30 minutes and resolved the same day. Most patients experiencing an IRR reported an event within or by the fourth infusion.

Aside from a lower frequency of ARIA-E and ARIA-H in the no-very low tau subgroup, the safety profile based on tau pathology was similar across no-very low tau, low-medium, and high-tau populations.

Proposed labeling includes warnings and precautions for ARIA-E and ARIA-H as well as for IRRs. Caution is also advised for use of thrombolytic therapy as symptoms of ARIA may be similar to those of stroke.

Overall, the safety profile of donanemab has been well characterized with risks similar to those observed for the class of amyloid-targeted therapies.

6.2.4.1. Analysis Approach

Lilly used 3 analysis sets to evaluate and describe the safety profile of donanemab:

1) the placebo-controlled data from Study AACI (referred to as AACI)
2) the integrated placebo-controlled data from Study AACI and Study AACG (referred to as Dona-PC), and
3) all data from patients exposed to donanemab (referred to as All Dona).

The safety of donanemab was evaluated primarily in the placebo-controlled portion of Study AACI and in integrated placebo-controlled analyses inclusive of the Phase 2 Study AACG and Phase 3 Study AACI. Because the safety profile of Studies AACI and AACG was consistent, results presented in this document will predominantly focus on the prespecified integrated safety outputs (Dona-PC). The prespecified safety analysis approach for each of the analysis sets summarizes data from the first dose of treatment to the end of the treatment period +57 days, corresponding to approximately 5 half-lives for donanemab. This analysis approach was aligned with FDA, prespecified in the integrated safety analysis plan, and consistent with the approach used by the FDA for other amyloid-targeting therapies.

Unless noted otherwise, all data presented are based on the prespecified approach.

6.2.4.2. Treatment Exposure

There are a total of 3101 patients in the overall safety analysis sets who received either donanemab or placebo.

A total of 2802 patients have received donanemab across the program and are included in the All Dona analysis set. Among these, 1057 patients had at least 12 months of exposure to donanemab at the proposed dosing regimen (that is, 3 infusions of 700 mg and at least 9 infusions of 1400 mg).

This is the largest registration safety database for an amyloid-targeting therapy, providing 3470 patient-years of observation.

A total of 984 patients received donanemab during placebo-controlled periods and are included in the Dona-PC analysis set. Among these, 524 patients had at least 12 months of exposure and 783 patients had at least 6 months of exposure at the proposed doing regimen, providing 1360 patient-years of observation.

6.2.4.3. Safety Population

6.2.4.3.1. Baseline Demographics for Safety Database

Collectively, compared to other contemporary AD clinical trials, the donanemab program enrolled an older and more clinically advanced population with higher disease burden including APOE ε4 carriers. These baseline characteristic differences are expected to have resulted in a population that is harder to treat from both a safety and efficacy perspective.

6.2.4.3.2. Concomitant Medications for Safety Database

Concomitant medications, including antithrombotic use, in the Phase 3 study are described in Section 6.2.2.3, and are similar in the Dona-PC and All Dona analysis sets.

6.2.4.4. Overall Summary of Adverse Events

Table 6.12 presents an overview of AEs for AACI, Dona-PC and All Dona.

In Dona-PC, the frequency of SAEs and TEAEs was similar between the placebo and donanemab treatment groups. There were more discontinuations from study treatment and from study in the donanemab group compared with placebo. Most discontinuations were due to IRRs or ARIA. There was also a higher frequency of death reported for donanemab-treated patients compared with placebo in Dona-PC analysis set. However, the frequency of deaths in All Dona was similar to the frequency observed in the placebo group of Dona-PC (Section 6.2.4.5).

Three of the deaths reported in the donanemab population were related to donanemab treatment. Specifically, 2 were reported as ARIA (1 ARIA-E and 1 ARIA-H) and 1 event reported as "Death" occurred in a patient with ongoing serious ARIA-E and ARIA-H. Beyond the 3 deaths associated with ARIA, no pattern or trend was reported in the type of event, timing, frequency, or nature of the events that led to death. Most were a single type of event, each presenting with multiple risk factors. The causes of death appeared to be primarily explained by patient age,

disease progression, comorbidities in patient medical history, and/or the use of confounding concomitant medications. More information on mortality is summarized in Section 6.2.4.5.

Table 6.12. Overview of Adverse Event Data, Donanemab Placebo-Controlled and All Dona Exposures, Integrated Analysis Sets, End of Study Treatment Period Plus 57 Days

	AACI N = 1727		Dona-PC N = 1983		All Dona
Data Cutoff Date	**14 April 2023**		**07 June 2023**		**07 June 2023**
	Placebo N = 874 n (%)	**Donanemab N = 853 n (%)**	**Placebo N = 999 n (%)**	**Donanemab N = 984 n (%)**	**Donanemab N = 2802 N (%)**
Deaths[b]	10 (1.1)	16 (1.9)	12 (1.2)	18 (1.8)	36 (1.3)
SAEs	138 (15.8)	148 (17.4)	153 (15.3)	170 (17.3)	463 (16.5)
DCAE	38 (4.3)	112 (13.1)	46 (4.6)	153 (15.5)	295 (10.5)
TEAEs	718 (82.2)	759 (89.0)	831 (83.2)	879 (89.3)	2260 (80.7)
ARIA-E/H[a,c]	130 (14.9)	314 (36.8)	142 (14.2)	365 (37.1)	917 (32.7)
ARIA-E[c]	18 (2.1)	205 (24.0)	19 (1.9)	240 (24.4)	571 (20.4)
Symptomatic ARIA-E[c]	1 (0.1)	52 (6.1)	1 (0.1)	57 (5.8)	127 (4.5)
ARIA-H[c]	119 (13.6)	268 (31.4)	130 (13.0)	309 (31.4)	778 (27.8)
Intracerebral hemorrhage >1 cm	2 (0.2)	3 (0.4)	2 (0.2)	3 (0.3)	10 (0.4)
IRR	4 (0.5)	74 (8.7)	4 (0.4)	84 (8.5)	234 (8.4)
Anaphylactic reaction	0 (0.0)	3 (0.4)	0 (0.0)	3 (0.3)	9 (0.3)

Abbreviations: AACI = I5T-MC-AACI; ARIA-E = amyloid-related imaging abnormalities–edema/effusions; ARIA-H = amyloid-related imaging abnormalities–hemorrhage/hemosiderin deposition; DCAE = discontinuation of study treatment due to adverse event; Dona = donanemab; IRR = infusion-related reaction; MRI = magnetic resonance imaging; n = number of patients with at least 1 adverse event; N = number of patients; PC = placebo controlled; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

a Patients may be counted in more than 1 category.

b Deaths are also included as SAEs and discontinuations due to adverse event and are discussed in Section 6.2.4.5.

c Based on MRI or TEAE cluster output.

During the Biologics License Application review, the FDA also evaluated these data using a different safety analysis approach, summarizing data from the first dose of treatment to the *last dose of study drug* +57 days. For comparison, Table 6.13 shows the results from the FDA approach taken during the review period next to the prespecified approach. The safety findings are similar regardless of the approach. As such, data presented in this document are based on the prespecified approach.

Table 6.13. Comparison of Safety Data Using Different Safety Analysis Approaches

	Prespecified Safety Analysis from the first dose of treatment to the *end of the treatment period* +57 days		**FDA Additional Analysis** from the first dose of treatment to the *last dose of study drug* +57 days	
	AACI N = 1727		**AACI N = 1727**	
Data Cutoff Date	**14 April 2023**		**07 June 2023**	
	Placebo N = 874 n (%)	**Donanemab N = 853 n (%)**	**Placebo N = 874 n (%)**	**Donanemab N = 853 n (%)**
Deaths[b]	10 (1.1)	16 (1.9)	7 (0.8)	16 (1.9)
SAEs	138 (15.8)	148 (17.4)	126 (14.4)	140 (16.4)
DCAE	38 (4.3)	112 (13.1)	32 (3.7)	109 (12.8)
TEAEs	718 (82.2)	759 (89.0)	715 (81.8)	758 (88.9)
ARIA-E/H[a,c]	130 (14.9)	314 (36.8)	126 (14.4)	311 (36.5)
ARIA-E[c]	18 (2.1)	205 (24.0)	18 (2.1)	204 (23.9)
Symptomatic ARIA-E[c]	1 (0.1)	52 (6.1)	0	52 (6.1)
ARIA-H[c]	119 (13.6)	268 (31.4)	115 (13.2)	264 (30.9)
Intracerebral hemorrhage >1 cm	2 (0.2)	3 (0.4)	2 (0.2)	3 (0.4)
IRR	4 (0.5)	74 (8.7)	4 (0.5)	74 (8.7)
Anaphylactic reaction	0 (0.0)	3 (0.4)	0 (0.0)	3 (0.4)

Abbreviations: AACI = I5T-MC-AACI; ARIA-E = amyloid-related imaging abnormalities–edema/effusions; ARIA-H = amyloid-related imaging abnormalities–hemorrhage/hemosiderin deposition; DCAE = discontinuation of study treatment due to an adverse event; IRR = infusion-related reaction; MRI = magnetic resonance imaging; n = number of patients with at least 1 adverse event; N = number of patients; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

[a] Patients may be counted in more than 1 category.

[b] Deaths are also included as SAEs and discontinuations due to AE. Mortality is more extensively discussed in Section 6.2.4.5.

[c] Based on MRI or TEAE cluster output.

6.2.4.4.1. Common Adverse Events

In Dona-PC, 89% of donanemab-treated patients had at least 1 TEAE compared with 83% of placebo-treated patients (Table 9.8).

The most common TEAEs for donanemab-treated patients included

- ARIA-E: 24%
- ARIA-H: 18%
- COVID-19: 14%
- Fall: 13%, and
- Headache: 13%.

Most common TEAEs in patients were mild to moderate. Severe TEAEs were reported by 13% of donanemab-treated patients and 10% of placebo-treated patients. ARIA-E was the most common severe event (2%) in patients.

Events of ARIA-E, ARIA-H, IRR, nausea, headache, and vomiting are considered ADRs based on the review of data and biological plausibility.

In All Dona, a similar pattern of common TEAEs was observed.

6.2.4.4.2. Serious Adverse Events

In Dona-PC, 17% of donanemab-treated patients reported 1 or more SAEs compared with 15% of placebo-treated patients.

There were no notable differences between treatment groups for any individual system organ class, except for Nervous system disorders. SAEs within Nervous system disorders were reported in 3% of placebo group and 5% of donanemab treatment group (Table 6.14). This difference was primarily driven by donanemab-treated patients reporting ARIA-E (1.5%) and ARIA-H (0.4%) compared with no patients in the placebo group reporting either of these as an SAE.

Other SAEs occurring in at least 1% of donanemab-treated patients were syncope and pneumonia.

In All Dona, 17% of donanemab-treated patients reported 1 or more SAEs. The only SAE that occurred in at least 1% of All Dona was ARIA-E.

Table 6.14. Serious Adverse Events Occurring in at Least 1% of Donanemab-Treated Patients, Including Incidence Rates Adjusted for Observation Time, by Preferred Terms within System Organ Class, Donanemab Analysis Sets

	AACI N = 1727		Dona-PC N = 1983		All Dona
Data Cutoff Date	**14 April 2023**		**07 June 2023**		**07 June 2023**
Number of Patients	**Placebo N = 874 n (%)**	**Donanemab N = 853 n (%)**	**Placebo N = 999 n (%) [IR][a]**	**Donanemab N = 984 n (%) [IR][a]**	**Donanemab N = 2802 n (%) [IR]**
Patients with ≥1 SAE	138 (15.8)	148 (17.4)	153 (15.3) [11.5]	170 (17.3) [13.6]	463 (16.5) [14.7]
Nervous system disorders	**28 (3.2)**	**40 (4.7)**	**29 (2.9) [2.1]**	**46 (4.7) [3.5]**	**123 (4.4) [3.6]**
ARIA-E	0	13 (1.5)	0	15 (1.5) [1.1]	32 (1.1) [0.9]
Syncope	13 (1.5)	9 (1.1)	11 (1.1) [0.8]	10 (1.0) [0.7]	26 (0.9) [0.8]
Infections and infestations	**28 (3.2)**	**25 (2.9)**	**31 (3.1) [2.2]**	**33 (3.4) [2.5]**	**97 (3.5) [2.8]**
Pneumonia	5 (0.6)	5 (0.6)	6 (0.6) [0.4]	10 (1.0) [0.7]	23 (0.8) [0.7]
COVID-19	4 (0.5)	9 (1.1)	4 (0.4) [0.3]	8 (0.8) [0.6]	18 (0.6) [0.5]

Abbreviations: AACI = I5T-MC-AACI; ARIA-E = amyloid-related imaging abnormalities–edema/effusions; COVID-19 = coronavirus disease 2019; Dona = donanemab; IR = incidence rates per 100 patient-years; n = number of patients with events meeting specified criteria; N = number of patients in the analysis population; PC = placebo controlled; SAE = serious adverse event.

a Observation time-adjusted incidence rate.

6.2.4.4.3. Adverse Events Leading to Treatment Discontinuation

Discontinuations from study treatment and from study were more frequent in the donanemab treatment group compared with the placebo group (Table 9.9). Most discontinuations were due to IRRs.

In Dona-PC, the most common AEs leading to treatment discontinuation among donanemab-treated patients were

- 4% IRRs
- 3% ARIA-E
- 1% superficial siderosis of the central nervous system, and
- 1% ARIA-H.

ARIA, intracerebral hemorrhage greater than 1 cm (referred to as macrohemorrhages), and hypersensitivity, including IRRs and anaphylaxis, are considered AEs of special interest and are

discussed further in Section 6.2.4.6 (ARIA and macrohemorrhages) and in Section 6.2.4.7 (IRRs).

In All Dona, a similar pattern of AEs leading to treatment discontinuation was observed.

6.2.4.5. Deaths

AD is a progressive disease that is not currently possible to reverse and is ultimately fatal. Severe dementia frequently causes complications and other comorbid conditions and can significantly increase risk of acute conditions that can cause death, such as pneumonia. When compared to patients without dementia, the risk of mortality for patients with AD is increased 3.7-fold (Liang et al. 2021).

Mortality was extensively evaluated across the donanemab clinical program. Regardless of the methodology, the findings are similar and conclusions are consistent. Beyond the known class-risk of ARIA with a low frequency of fatal events (0.3%), there is no evidence of an increase in risk of mortality or excess death related to donanemab treatment.

Pre-Specified Mortality Analysis

Mortality was initially evaluated according to the pre-specified integrated safety analysis plan in Dona-PC that accounted for adverse events leading to death occurring within the placebo-controlled period. This pre-specified approach, which is consistent with previous studies conducted in the early symptomatic AD space, considers a patient at risk for death from date of the first dose through end of treatment period plus 57 days, or until study discontinuation. Using this approach, there were 18 (1.8%) deaths reported for donanemab-treated patients and 12 (1.2%) for placebo, a 0.63% difference, 95% CI: (-0.45%, 1.7%) (Table 6.15). Sensitivity analyses were also conducted (Table 9.11).

Table 6.15. Risk of Fatal Outcomes in Donanemab Placebo-Controlled Analysis Sets: Prespecified 07 June 2023

	AACI -PC		Dona-PC	
	Placebo (N = 874)	**Dona (N = 853)**	**Placebo (N = 999)**	**Dona (N = 984)**
Death				
N	10	17	12	18
Frequency (%)	1.14	1.99	1.2	1.83
95% CI	0.44, 1.85	1.06, 2.93	0.53, 1.88	0.99, 2.67
Risk difference (95% CI)	--	0.85 (-0.32, 2.02)	--	0.63 (-0.45, 1.7)
Odds ratio (p-value) [a]	--	1.76 (0.177)	--	1.53 (0.25)
Death (excluding ARIA death)[b]				
N	10	14	12	15
Frequency (%)	1.44	1.64	1.20	1.52
95% CI	0.44, 1.85	0.79, 2.49	0.53, 1.88	0.76, 2.29
Risk difference (95% CI)	--	0.5 (-0.61, 1.6)	--	0.32 (-0.7, 1.34)
Odds ratio (p-value)	--	1.44 (0.416)	--	1.27 (0.533)

Abbreviations: AACI = I5T-MC-AACI; ARIA = amyloid-related imaging abnormalities; CI = confidence interval; Dona = donanemab; LTE = long-term extension; n = number of patients with adverse event leading to death; N = number of patients in the treatment group; PC = placebo controlled.

[a] Mantel-Haenszel odds ratio stratified by study. LY3002813 is numerator, placebo is denominator.

[b] Deaths related to ARIA in 3 patients in Study AACI were excluded.

Note: Participants were included from the first dose of treatment to the end of treatment period +57 days, or the day prior to the first LTE visit, whichever occurs first.

A comprehensive medical review of deaths occurring during the placebo-controlled period of the studies (Dona-PC) where cause of death as reported was performed and is summarized in Section 9.1. Three of the deaths in the donanemab population were related to donanemab treatment. Specifically, 2 events were reported as ARIA (1 ARIA-E and 1 ARIA-H) and 1 event reported as "Death" occurred in a patient with ongoing serious ARIA-E and ARIA-H. Beyond the 3 deaths associated with ARIA, no pattern or trend was reported in the type of event, timing, frequency, or nature of the events that led to death (Table 9.1). Most were a single type of event, each presenting with multiple risk factors. The causes of death appeared to be primarily explained by patient age, disease progression, comorbidities in patient medical history, and/or the use of confounding concomitant medications. The medical review of cases and conclusions is consistent irrespective of the methodology employed. The number of deaths for causes other than ARIA was similar across placebo and donanemab (n = 15 in the donanemab group and n = 12 in the placebo group). A summary of the adverse events leading to death by preferred term within system organ class is in Table 9.1 along with a discussion of the events noted in the donanemab-treated group and patient narratives are included (Section 9.1).

Beyond the placebo-controlled dataset, among any patient receiving donanemab (All Dona), the frequency of death reported using the pre-specified method in donanemab-treated patients (1.3%, 1.04/100 PYO) is similar to the frequency for placebo-treated patients from the placebo-controlled period (1.2%, 0.8/100 PYO). This demonstrates that as exposure to donanemab was expanded with patients from the separate addendum, the frequency of death did not increase.

Updated Mortality Analysis According to Most Recent FDA Feedback

Given that donanemab treatment duration was individualized in both AACG and AACI, a variety of different analyses were conducted to further clarify the mortality percentage across treatment groups in accordance with FDA requests. These analyses demonstrated broadly consistent results (Table 6.16).

In advance of this advisory committee meeting, the FDA proposed a methodology that considered any death that occurred during the timeframe from first dose to 76 weeks, irrespective of whether the patient was still on active treatment or had withdrawn from the study. In this analysis, fatal events were assigned to the initial treatment the patient received, even if the patient had completed treatment due to plaque clearance and was switched to placebo or if they had discontinued treatment or study entirely.

Vital Status Assessment

Responsive to FDA's requests and to further support this methodology, Lilly conducted a vital status assessment for AACI through a third-party for patients whose vital status was unknown at study completion (i.e., patients who were lost-to-follow up or had withdrawn from the study). This evaluation was limited to countries where follow up is legally permissible and to sites that agreed to this follow-up.

In total, vital status has been confirmed for 1555 of 1727 patients who received a dose of study drug in AACI, representing 90% of treated patients and providing reasonable resolution of any potential uncertainty for mortality analyses.

As of 09 May 2024, the majority of patients across both the donanemab and placebo treatment groups in AACI were alive.

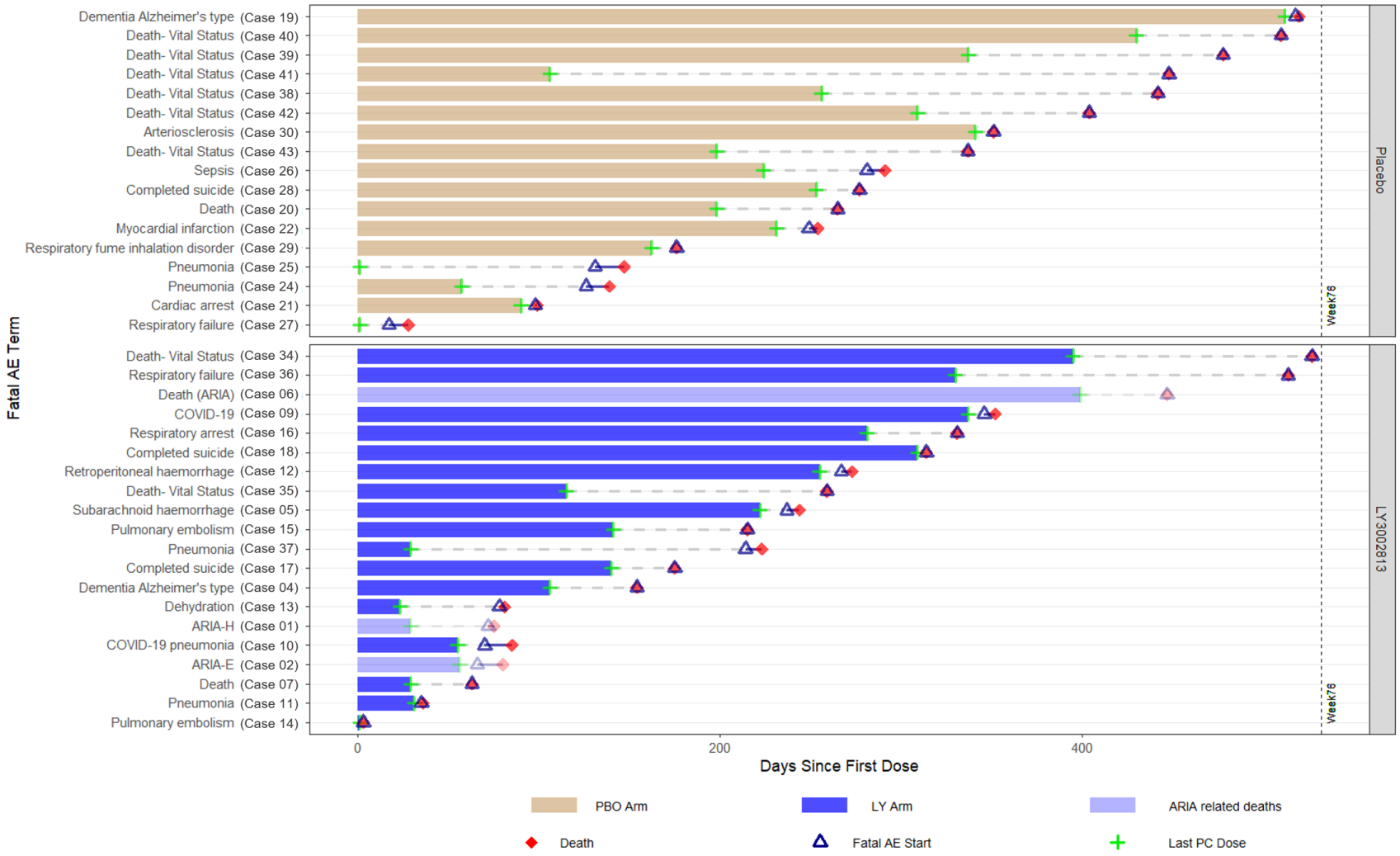
- Vital status was confirmed for 18 of the 22 patients lost to follow-up; 1 donanemab- and 3 placebo-treated patients are still missing.
    - Out of the 22 patients, there were 4 confirmed deaths: 2 from the donanemab group and 2 from the placebo group. One of these events, from the placebo group, occurred within 76 weeks of the initial dose. None had ongoing ARIA at the last known MRI prior to loss to follow-up.
- Vital status was confirmed for 184 of the 352 patients who discontinued after receiving a dose of study drug. Vital assessment follow-up was not available for 80 donanemab- and 88-placebo treated patients due to reasons including, different country regulatory and/or legal requirements (for participants located in the Czech Republic, Japan, Netherlands, and Poland) and because sites/participants did not agree to this assessment.
    - Out of the 184 patients, there were 26 confirmed deaths: 12 from the donanemab group and 14 from the placebo group. Two of these events from the donanemab group, and 5 from the placebo group occurred within 76 weeks of initial dose. No patients in the donanemab group and 3 patients in the placebo group had ongoing ARIA at the last known MRI prior to withdrawal.

Incorporating vital status information into Dona-PC for all patients within 76 weeks of treatment, there were 20 (2.0%) deaths reported for donanemab-treated patients and 17 (1.7%) for placebo. Aside from the 3 ARIA-related deaths, there were 17 (1.7%) non-ARIA related deaths reported for donanemab-treated patients and 17 (1.7%) for placebo (Table 1.4).

The cumulative incidence of death at 76 weeks was estimated using Kaplan-Meier methods and the Cox Proportional Hazards Model shows a HR (95% CI) of 1.2 (0.63 – 2.33) for all reported deaths and 1.0 (0.52-2.02) for non-ARIA deaths (Figure 1.6). Sensitivity analyses to investigate the HR and incidence ratio were conducted and demonstrated similar results (Table 9.12).

There are limitations to this analysis including remaining missing information for 10% of the overall randomized population in AACI. Causes of death for newly identified cases through this methodology are also not available for further medical review.

Figure 6.11 lists and depicts the timing of deaths occurring within 76 weeks of the first dose in the mortality analyses.



Abbreviations: AE = adverse event; ARIA = amyloid-related imaging abnormalities; COVID-19 = coronavirus disease 2019; Dona = donanemab; PBO = placebo; PC = placebo controlled.

Figure 6.11. Visualization of timing of all fatal events occurring within 76 weeks.

Table 6.16. Comparison of Mortality Data Using Different Analysis Approaches

	Prespecified Safety Analysis from the first dose of treatment to the *end of the treatment period* +57 days		**Additional Analysis** from the first dose of treatment *through 76 weeks*		**Additional Analysis** from the first dose of treatment *through 76 weeks with vital status update*	
	Dona-PC N = 1983		**Dona-PC N = 1983**		**Dona-PC N = 1983**	
Data Cutoff	**07 June 2023**		**07 June 2023**		**09 May 2024**	
	Placebo N = 999 n (%)	**Dona N = 984 n (%)**	**Placebo N = 999 n (%)**	**Dona N = 984 n (%)**	**Placebo N =999 n (%)**	**Dona N=984 n (%)**
Deaths	12 (1.2)	18 (1.8)	11 (1.1)	18 (1.8)	17 (1.7)	20 (2.0)

Abbreviations: AACI = I5T-MC-AACI; Dona = donanemab; n = number of patients with events meeting specified criteria; N = number of patients in the analysis population; PC = placebo controlled.

6.2.4.5.1. Review of Death Cases

A summary of fatal events occurring within 76 weeks of first dose is provided in Table 6.17.

Table 6.17. Death, Incidence Adjusted for Observation Time, occurring within 76 weeks

	AACI N = 1727		Dona-PC N = 1983	
Data Cutoff Date	**07 June 2023**		**07 June 2023**	
System Organ Class Preferred Term	**Placebo N = 874 PYO = 1205.1 n (%) [IR]**	**Donanemab N = 853 PYO = 1171.2 n (%) [IR]**	**Placebo N = 999 PYO = 1365.8 n (%) [IR]**	**Donanemab N = 984 PYO = 1340.1 n (%) [IR]**
Subjects with ≥1 Fatal AE	16 (1.8) [1.3]	19 (2.2) [1.6]	17 (1.7) [1.2]	20 (2.0) [1.5]
Cardiac disorders	1 (0.1) [0.1]	0	2 (0.2) [0.1]	0
Cardiac arrest	0	0	1 (0.1)	0
Myocardial infarction	1 (0.1)	0	1 (0.1)	0
Gastrointestinal disorders	0	1 (0.1) [0.1]	0	1 (0.1) [0.1]
Retroperitoneal hemorrhage	0	1 (0.1)	0	1 (0.1)
General disorders and administration site conditions	7 (0.8) [0.6]	4 (0.5) [0.3]	7 (0.7) [0.5]	4 (0.4) [0.3]
Death	1 (0.1)	2 (0.2)[a]	1 (0.1)	2 (0.2)[a]
Death-Vital Status Update	6 (0.7)	2 (0.2)	6 (0.6)	2 (0.2)
Infections and infestations	3 (0.3) [0.2]	3 (0.4) [0.3]	3 (0.3) [0.2]	4 (0.4) [0.3]
COVID-19	0	1 (0.1)	0	1 (0.1)
COVID-19 pneumonia	0	1 (0.1)	0	1 (0.1)
Pneumonia	2 (0.2)	1 (0.1)	2 (0.2)	2 (0.2)
Sepsis	1 (0.1)	0	1 (0.1)	0
Injury, poisoning, and procedural complications	1 (0.1) [0.1]	0	1 (0.1) [0.1]	0
Respiratory fume inhalation disorder	1 (0.1)	0	1 (0.1)	0
Metabolism and nutrition disorders	0	1 (0.1) [0.1]	0	1 (0.1) [0.1]
Dehydration	0	1 (0.1)	0	1 (0.1)
Nervous system disorders	1 (0.1) [0.1]	4 (0.5) [0.3]	1 (0.1) [0.1]	4 (0.4) [0.3]
ARIA-E	0	1 (0.1)	0	1 (0.1)
ARIA-H	0	1 (0.1)	0	1 (0.1)
Dementia Alzheimer's type	1 (0.1)	1 (0.1)	1 (0.1)	1 (0.1)
Subarachnoid hemorrhage	0	1 (0.1)	0	1 (0.1)
Psychiatric disorders	1 (0.1) [0.1]	2 (0.2) [0.2]	1 (0.1) [0.1]	2 (0.2) [0.1]
Completed suicide	1 (0.1)	2 (0.2)	1 (0.1)	2 (0.2)
Respiratory, thoracic, and mediastinal disorders	1 (0.1) [0.1]	4 (0.5) [0.3]	1 (0.1) [0.1]	4 (0.4) [0.3]
Pulmonary embolism	0	2 (0.2)	0	2 (0.2)
Respiratory arrest	0	1 (0.1)	0	1 (0.1)
Respiratory failure	1 (0.1)	1 (0.1)	1 (0.1)	1 (0.1)
Vascular disorders	1 (0.1) [0.1]	0	1 (0.1) [0.1]	0
Arteriosclerosis	1 (0.1)	0	1 (0.1)	0

Abbreviations: AACI = I5T-MC-AACI; AE = adverse event; ARIA-E = amyloid-related imaging abnormalities–edema/effusions; ARIA-H = amyloid-related imaging abnormalities–hemorrhage/hemosiderin deposition; CI = confidence interval; COVID-19 = coronavirus disease 2019; IR = incidence rate; LTE = long-term extension; n = number of patients within the particular category adverse event; N = number of patients in the analysis population; PC = placebo controlled; SAE = serious adverse event.

[a] Includes the additional participant who died with ongoing SAE of ARIA-E.
Note: Participants were included from the first dose of treatment to 76 weeks irrespective of patient disposition and incorporated the results of vital status searches from Study AACI

Based on the deaths occurring within 76 weeks of first dose, 3 of the deaths reported in the donanemab-treated group were related to donanemab treatment. Specifically, 2 were reported as ARIA (1 ARIA-E and 1 ARIA-H) and 1 event reported as "Death" occurred in a patient with ongoing serious ARIA-E and ARIA-H. The number of deaths for causes other than ARIA was similar across placebo and donanemab (n = 17 in the donanemab group and n = 17 in the placebo group).

Further review of the individual events in the donanemab-treated arm in the PC period by decreasing frequency showed

- 4 events in the General disorders and administration site conditions SOC compared to 7 events in placebo-treated patients:
  - 1 associated with ARIA that was discussed above
  - 1 patient who died in her sleep with a previous nonserious AE of peripheral edema, and
  - 2 patients were identified from the vital status search with death occurring 132 or 145 days after the last dose of donanemab and with cause of death not provided. In the placebo group, 6 patients were identified with cause of death not provided.
- 4 events in the Infections and infestations SOC compared to 3 events in placebo-treated patients:
  - 2 events of pneumonia for the donanemab-treated arm compared to 2 events in placebo-treated patients. 1 donanemab-treated patient had pneumonia possibly due to aspiration. Another patient that discontinued due to hypersensitivity upon second infusion developed pneumonia and died 195 days after last dose of donanemab.
  - 1 event of COVID 19 and 1 event of COVID 19 pneumonia were reported in the donanemab treatment arm which would not be unexpected during the pandemic in an AD population.
- 4 events in the Nervous system disorders SOC compared to 1 in placebo-treated patients:
  - 1 fatal ARIA H and 1 fatal ARIA H discussed above- both related to donanemab
  - 1 subarachnoid hemorrhage after a fall in a patient who was randomly assigned to donanemab and had received 2 infusions of saline after meeting amyloid clearance in Dona-PC, and
  - 1 event of Dementia Alzheimer's type after multiple SAEs of erosive gastritis and esophagitis compared to 1 placebo patient dying from this event.

- 4 events in donanemab-treated patients in Respiratory, thoracic and mediastinal disorders SOC compared to 1 placebo-treated patient:
    - 2 patients died from a pulmonary embolism where each had multiple risk factors
    - 1 patient died from respiratory arrest 50 days after the last dose of donanemab, likely as a complication of multi-factorial illness
    - 1 patient died from respiratory failure 184 days after the last dose of donanemab and after pneumonia. In the placebo-treated group, 1 patient also died from respiratory failure.
- 2 suicides in the donanemab group compared with 1 suicide in the placebo group, and
- all other deaths were a single type of event in patients with risk factors.

An evaluation of the fatal events beyond those related to ARIA were primarily explained by patient age, disease progression, comorbidities in patient medical history, the use of confounding concomitant medications and/or were long after (more than 5 half-lives) donanemab treatment. Most events presented with multiple risk factors. Beyond the 3 deaths associated with ARIA, the other events in the donanemab group had no discernible pattern or trend in the type of event, timing, frequency, or nature of the events that led to death, and all were assessed as not related to donanemab by the study investigator.

Additional information for each death is summarized in Appendix 9.2.

6.2.4.5.2. Additional Mortality Considerations

To further understand the impact of donanemab on mortality, additional supportive analyses were conducted.

Mortality risk for placebo patients switched to donanemab

One approach evaluated patients randomly assigned to placebo in Study AACI who went on to receive donanemab in the long-term extension (n = 645). Using this approach, mortality among patients who switched treatment was 0.5% (3/645; 1.4/100 PYO). One of these 3 deaths was due to ARIA-E (0.16%).

The overall mortality frequency was lower for this donanemab-treated subgroup than that noted for donanemab-treated patients in the PC period and ARIA mortality is similar to that for donanemab-treated group from the PC period.

Mortality risk by ever exposure to donanemab

Another approach evaluated patients in 2 groups:

- **Never** received donanemab throughout a study (n = 299), or
- **Ever** received donanemab at any time of a study (n = 2802).

Using this approach, 4.3% of the patients never receiving donanemab died compared to 1.4% of the patients who were ever exposed to donanemab (Figure 9.7).

Observation-time adjusted incidence rates for deaths were also calculated given the large difference in observation time between the treatment groups: 3.8 per 100 patient-years (95% CI: 2.0, 6.5) for patients who never received donanemab compared with 0.9 per 100 patient-years (95% CI: 0.6, 1.2) for patients who ever received donanemab. This results in an incidence ratio of 0.22 (95% CI: 0.12, 0.42; p-value ≤0.001). Lilly acknowledges the limitations to this analysis as the placebo-treated patients who did not ever switch to receive donanemab may have been at a higher baseline overall risk of death. Nevertheless, the results do not support a potential impact of donanemab on mortality.

Higher placebo death incidence in donanemab clinical trial versus other contemporary AD clinical trials

The frequency and incidence rate of mortality in placebo-treated patients in the donanemab clinical program are higher than what has been reported in other contemporary clinical programs for amyloid-targeting therapies. For example, the placebo mortality frequency in the pre-specified Dona-PC analysis set of 1.2% is higher than in other studies of FDA-approved amyloid-targeting therapies, which ranged from 0.5% to 0.8% (Budd Haeberlein et al. 2022; van Dyck et al. 2023). This could reflect differences in baseline demographics for the donanemab studies including older age, higher number of comorbidities permitted in the study, worse clinical scores at baseline, more advanced clinical stage, greater frequency of APOE ε4 carriers, more MRI pathologies including cortical superficial siderosis, higher amyloid pathology, and higher tau pathology than the comparative approved therapies. These baseline characteristic differences are expected to have resulted in a population that was both harder to treat and more susceptible to both drug-related and other unrelated AEs or death due to comorbid illness. Given these factors and publications showing that mortality rates increase as a function of AD severity (Steenland et al. 2010), higher death rates would be expected in the donanemab clinical trial program versus other contemporary AD clinical trials (Steenland et al. 2010).

Despite higher observed mortality rates versus other contemporary AD clinical trials, the frequencies and incidence rates of mortality for both placebo- and donanemab-treated patients are lower than what is reported in the literature for this AD population. Incidence rates of death among patients without dementia have been reported as 1.6 per 100 patient-years compared to 4.3 in patients newly diagnosed with MCI and 10.6 per in patients newly diagnosed with AD (Steenland et al. 2010). For descriptive comparison, incidence rates of death observed in Dona-PC ranged from 0.8 to 1.3 deaths per 100 patient-years, which is lower even than the rates expected for individuals without cognitive impairment (Table 9.11)

Risk factors and mortality

A univariate analysis, conducted by applying log rank test on treatment and 23 baseline variables, was conducted to evaluate potential contributing factors to mortality from the Dona-PC analysis set. The outcome revealed 5 variables that were initially significant: age, presence of superficial siderosis, history of diabetes, nonaspirin antiplatelet usage, and severity of AD clinical status. After applying a postvariable false discovery rate correction, only age remained as the sole statistically significant variable (Table 6.18 and Table 9.10).

Table 6.18. Univariate Analysis with FDR Correction

Variable Description	p-Value	FDR-Adjusted p-Value
Age group	<0.001	0.003
Presence superficial siderosis (Y/N)	0.006	0.055
History of diabetes	0.007	0.055
Nonaspirin antiplatelet usage	0.009	0.055
Disease severity status (MCI, mild, moderate)	0.019	0.089

Abbreviations: FDR = false discovery rate; MCI = mild cognitive impairment; N = no; Y = yes.

This analysis did not identify treatment as highly impactful; rather, treatment was among the least impactful variables. Other variables or combinations thereof appeared to have a larger influence on mortality than treatment. Nevertheless, the limited number of total deaths, and even fewer ARIA-related deaths (n = 3) associated with treatment, preclude definitive conclusions.

6.2.4.5.3. Mortality Conclusions

The review of clinical trial data shows an overall low frequency of fatal AEs, regardless of analysis methodology. Beyond the 3 deaths associated with ARIA and related to donanemab treatment, no pattern or trend was reported in the type of event, timing, frequency, or nature of the events that led to death (Table 6.17). Most were a single type of event, each presenting with multiple risk factors. The causes of death appeared to be primarily explained by patient age, disease progression, comorbidities in patient medical history, and/or the use of confounding concomitant medications.

Incorporating vital status information for all patients as of 9 May 2024 in the 76-week treatment period irrespective of whether the patient was still on active treatment or had withdrawn from the study, there were 20 (2.0%) deaths reported for donanemab-treated patients and 17 (1.7%) for placebo. Aside from the 3 ARIA-related deaths, there were 17 (1.7%) non-ARIA related deaths reported for donanemab-treated patients and 17 (1.7%) for placebo.

An analysis of risk factors suggests that age had a significant association with death, with other risk factors playing a possible role including the presence of superficial siderosis, a history of diabetes, baseline use of nonaspirin antiplatelets, and baseline disease severity. Many other variables, including treatment with donanemab, were not found to impact mortality, although the sample size is small. The absolute difference in risk of death between donanemab-treated and placebo-treated patients was consistently low across analysis methods, especially after accounting for the ARIA-related deaths associated with donanemab.

Regardless of methodology employed, the comprehensive medical review of the individual fatal cases confirmed an association between donanemab and ARIA-related deaths and does not suggest a possible causal association between the remaining fatal events.

Safety events that are rare or uncommon cannot be fully characterized in a typical randomized controlled study due to limited sample size and short exposure duration. Further characterization of these safety events is best suited for a postmarketing setting (Section 7).

6.2.4.6. Amyloid-Related Imaging Abnormalities

6.2.4.6.1. Overview of ARIA-E and ARIA-H

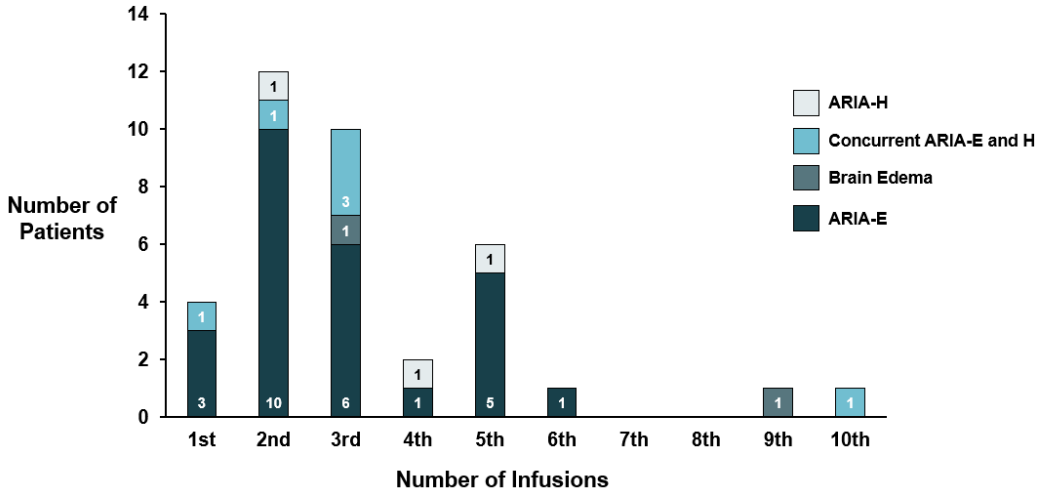
ARIA is characterized as either ARIA with edema (ARIA-E), which can be observed on MRI as brain edema or sulcal effusions, or ARIA with hemosiderin deposition (ARIA-H), which includes microhemorrhage and superficial siderosis.

ARIA can be found in patients with AD, particularly in patients with MRI findings suggestive of cerebral amyloid angiopathy, such as pretreatment microhemorrhage or superficial siderosis. ARIA-H is often concurrent with ARIA-E although it can also be found alone.

ARIA manifested as ARIA-E and ARIA-H are the primary on-target adverse effects of this generation of amyloid-targeting therapies. Table 6.19 presents an overview of ARIA-related events for AACI, Dona-PC, and All Dona and includes intracerebral hemorrhage greater than 1 cm.

ARIA was reported more frequently (37%) for donanemab-treated patients compared with placebo-treated patients (14%). Most ARIA events were mild to moderate in radiographic severity, nonserious, and asymptomatic (Section 6.2.4.6.2, Section 6.2.4.6.3, and Table 6.19). Most serious ARIA occurred early in the treatment period and fatal ARIA-E or ARIA-H (0.2%) occurred uncommonly. A total of 3 donanemab-treated patients had serious ARIA and subsequently died (see Section 6.2.4.5).

Most ARIA events were first observed within 24 weeks (6th infusion) of treatment, and most serious ARIA events were observed within 12 weeks (3rd infusion) of treatment initiation (Figure 6.12).



Abbreviations: ARIA = amyloid-related imaging abnormalities; ARIA-E = amyloid-related imaging abnormalities-edema/effusions; ARIA-H = amyloid-related imaging abnormalities–hemorrhage/hemosiderin deposition; SAE = serious adverse event.
Timing of first/new ARIA SAE with the number of patients with a SAE of ARIA on the y-axis and number of infusions they received on the x-axis.
All Dona analysis set, data cutoff date: 07 June 2023.

Figure 6.12. ARIA-related SAEs (All Dona Analysis Set).

More symptomatic ARIA-E/H, and serious ARIA-E/H was found among donanemab-treated APOE ε4 carriers compared with noncarriers (Sections 6.2.4.6.2 and 6.2.4.6.3) and frequencies were higher for APOE ε4 homozygotes compared with heterozygotes.

ARIA-E and ARIA-H were also more frequent for donanemab-treated patients with pretreatment MRI findings of microhemorrhage and/or superficial siderosis.

The frequency of ARIA-E or ARIA-H for donanemab-treated patients using antithrombotic medications (at any time or within 30 days prior to the event) was similar to those not using antithrombotic medications (Section 6.2.4.6.5).

Table 6.19. Overview of ARIA-Related Events, Donanemab Placebo-Controlled and All Dona Analysis Sets, End of Treatment Period Plus 57 Days

	AACI N = 1727		Dona-PC N = 1983		All Dona
	14 April 2023		07 June 2023		07 June 2023
	Placebo N = 874 n (%)	Donanemab N = 853 n (%)	Placebo N = 999 n (%)	Donanemab N = 984 n (%)	Donanemab N = 2802 n (%)
ARIA total events[a,e]	130 (14.9)	314 (36.8)	142 (14.2)	365 (37.1)	917 (32.7)
Deaths	0 (0.0)	2 [d] (0.2)	0	2[d] (0.2)	3[d] (0.1)
SAEs[e]	0 (0.0)	14 (1.6)	0	16 (1.6)	37 (1.3)
Treatment discontinuations	6 (0.7)	31 (3.6)	8 (0.8)	50 (5.1)	96 (3.4)
ARIA-E[e]	18 (2.1)	205 (24.0)	19 (1.9)	240 (24.4)	571 (20.4)
Deaths[b]	0 (0.0)	1 (0.1)	0	1 (0.1)	2 (0.1)
SAEs[e]	0 (0.0)	13 (1.5)	0	15 (1.5)	34 (1.2)
Study withdrawal	2 (0.2)	9 (1.1)	3 (0.3)	11 (1.1)	24 (0.9)
Treatment discontinuations	3 (0.3)	21 (2.5)	4 (0.4)	28 (2.8)	54 (1.9)
Symptomatic [c,e]	1 (0.1)	52 (6.1)	1 (0.1)	57 (5.8)	127 (4.5)
ARIA-H[e]	119 (13.6)	268 (31.4)	130 (13.0)	309 (31.4)	778 (27.8)
Deaths[b]	0 (0.0)	1 (0.1)	0	1 (0.1)	1 (0.0)
SAEs [e]	0 (0.0)	4 (0.5)	0	4 (0.4)	9 (0.3)
Study withdrawal	1 (0.1)	6 (0.7)	1 (0.1)	11 (1.1)	15 (0.5)
Treatment discontinuations	3(0.3)	10 (1.2)	4 (0.4)	22 (2.2)	42 (1.5)
Symptomatic[c,e]	3 (0.3)	10 (1.0)	3 (0.3)	10 (1.0)	15 (0.5)
Intracerebral hemorrhage >1 cm	2 (0.2)	3 (0.4)	2 (0.2)	3 (0.3)	10 (0.4)
Deaths[b]	0	0	0	0	0
SAE	1 (0.1)	1 (0.1)	1 (0.1)	1 (0.1)	3 (0.1)
Study withdrawal	1 (0.1)	0 (0.0)	1 (0.1)	0	0
Treatment discontinuations	1 (0.1)	2 (0.2)	1 (0.1)	2 (0.2)	6 (0.2)

Abbreviations: AE = adverse event; ARIA = amyloid-related imaging abnormalities; ARIA-E = amyloid-related imaging abnormalities–edema/effusions; ARIA-H = amyloid-related imaging abnormalities–hemorrhage/hemosiderin deposition; CRF = case report form; Dona = donanemab; LTE = long-term extension; MRI = magnetic resonance imaging; n = number of patients with at least 1 AE; N = number of patients; PC = placebo controlled; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

[a] Patients may be counted in more than 1 category.

[b] Deaths are also included in SAEs and discontinuations due to an AE.

[c] Based on ARIA CRF for ARIA-E or AE reporting for ARIA-H.

[d] Does not include the fatal case of "Death" where the event was not attributed to ARIA but was preceded by serious ARIA.

[e] Based on MRI or TEAE cluster output.

Note: Patients are followed from the first dose of treatment to the end of treatment period +57 days, or the day prior to the first LTE visit, whichever occurs first

Direct comparison of ARIA-E and ARIA-H between aducanumab and donanemab

While cross study comparisons of ARIA are challenging given the differences in baseline characteristics and pathologic disease burden, Lilly conducted a head-to-head study with aducanumab. In this 18-month, open-label, parallel-group, 2-arm head-to-head biomarker study (Study AACN) with aducanumab, the risk of ARIA was numerically lower for patients treated with donanemab (Salloway et al. 2024) and similar to what was observed in Study AACI.

Table 6.20. ARIA Safety Profile at 18 Months (Aducanumab vs Donanemab)

	Aducanumab (N = 69)	**Donanemab (N = 71)**
ARIA-E or ARIA-H, n (%)[a]	28 (40.6)	21 (29.6)
Serious ARIA-E	2 (2.9)	1 (1.4)[c]
ARIA-E[a]	24 (34.8)	17 (23.9)
Symptomatic[a]	5 (7.2)	2 (2.8)
ARIA-H[a,b]	23 (33.3)	16 (22.5)
Symptomatic[a,b]	1 (1.4)	1 (1.4)

Abbreviations: ARIA = amyloid-related imaging abnormalities; ARIA-E = amyloid-related imaging abnormalities-edema/effusions (also known as vasogenic edema); ARIA-H = amyloid-related imaging abnormalities-hemorrhage/hemosiderin deposition (including brain microhemorrhages and superficial siderosis); MRI = magnetic resonance imaging; TEAE = treatment-emergent adverse event.

[a] Based on MRI or TEAE cluster.

[b] ARIA-H includes microhemorrhage and superficial siderosis.

[c] Reported as brain edema.

In this study the primary endpoint at 6 months significantly greater amyloid plaque clearance was achieved for the donanemab group at 6 months (-62.1 +/- 3.7 CL for donanemab vs -16.4 +/- 3.8 CL for aducanumab) with a comparable frequency of total ARIA (25.4%) for donanemab-treated patients compared to aducanamab (26.1%) (Salloway et al. 2022). At 18 months, amyloid

plaque clearance was -84.2 CL with donanemab and -72.2 CL with aducanumab and total ARIA frequency further separated of 29.6% donanemab and 40.6% aducanumab (Salloway et al. 2024).

6.2.4.6.2. ARIA-E

ARIA-E was reported in 24.4% of donanemab-treated patients compared with 1.9% of placebo-treated patients (Table 6.19).

The frequency of ARIA-E in donanemab-treated patients was higher for APOE ε4 carriers than noncarriers (Table 6.21).

Table 6.21. Frequency of ARIA-E by APOE ε4 Carrier Status Based on MRI, Dona-PC, End of Treatment Period Plus 57 Days

	Dona-PC N = 1983	
	07 June 2023	
	Placebo N = 999 n/n1 (%)	Donanemab N = 984 n/n1 (%)
ARIA-E		
APOE ε4 homozygous carriers	6/174 (3.4)	69/168 (41.1)
APOE ε4 heterozygous carriers	9/538 (1.7)	124/522 (23.8)
Noncarrier	2/282 (0.7)	43/291 (14.8)
Severe ARIA-E		
APOE ε4 homozygous carriers	0	7/168 (4.2)
APOE ε4 heterozygous carriers	0	11/522 (2.1)
Noncarrier	0	3/291 (1.0)
Serious ARIA-E[a]		
APOE ε4 homozygous carriers	0	5/168 (3.0)
APOE ε4 heterozygous carriers	0	9/522 (1.7)
Noncarrier	0	1/291 (0.3)

Abbreviations: APOE ε4 = allele subtype 4 of the gene coding for apolipoprotein class E; ARIA-E = amyloid-related imaging abnormalities-edema/effusions; Dona = donanemab; MRI = magnetic resonance imaging; n = number of patients within each specified category; N = number of patients in the analysis population; n1 = number of patients in the analysis population ; PC = placebo controlled.

[a] Based on MRI or TEAE cluster

Among patients with ARIA-E, the proportion with a maximum radiographic severity using a 3-point scale was

- 29% mild
- 62% moderate, and
- 9% severe.

ARIA-E SAEs were reported for 15 (1.5%) donanemab-treated patients (Table 6.19) in Dona-PC, and 14 of the 15 SAEs were symptomatic. Most had resolution of all symptoms.

One death was reported due to ARIA-E (Case 2 Dona-PC) and another death was reported in a participant with ongoing serious ARIA-E (Case 6 Dona-PC). These cases are discussed in Section 6.2.4.5, with further details available in Appendix 9.1.

Symptomatic ARIA-E was reported in 6% of all donanemab-treated patients in Dona-PC. Symptoms included headache (10%), confusion (5%), dizziness (2%), nausea (2%), and seizure (2%).

For most donanemab-treated patients with ARIA-E, 55% had their first event detected by Week 12, and 88% by Week 24 with a median time to radiographic resolution of 59 days (range 15 to 292 days). Most ARIA-E events were managed by temporary interruption or permanent discontinuation with or without the use of supportive treatment.

Most of the donanemab-treated patients with ARIA-E had only 1 episode of ARIA-E (19%), followed by those with only 2 episodes of ARIA-E (4%). A maximum of 4 episodes was observed in 0.6% of patients in the donanemab-treated group. No placebo-treated patients had more than 1 episode of ARIA-E.

Results from All Dona analyses evaluating ARIA-E were consistent with those observed in Dona-PC. One additional death due to symptomatic ARIA-E was reported in a patient from Study AACI-LTE. This patient was originally randomized to placebo in the AACI period.

6.2.4.6.3. ARIA-H

ARIA-H was reported for 31% of donanemab-treated patients compared with 13% of placebo-treated patients (Table 6.19). Based on MRI, frequencies for the following types of ARIA-H were

- microhemorrhages
  - 10.9% of placebo group, and
  - 25.1% of donanemab treatment group, and
- superficial siderosis
  - 2.9% of placebo group, and
  - 16.1% of donanemab treatment group.

A higher frequency of ARIA-H was found for APOE ε4 carriers than noncarriers (Table 6.22).

Table 6.22. Frequency of ARIA-H by APOE ε4 Carrier Status Based on MRI, Dona-PC, End of Treatment Period Plus 57 Days

	Dona-PC N = 1983	
	07 June 2023	
	Placebo N = 999 n/n1 (%)	Donanemab N = 984 n/n1 (%)
ARIA-H		
APOE ε4 homozygous carriers	33/174 (19.0)	91/168 (54.2)
APOE ε4 heterozygous carriers	61/538 (11.3)	161/522 (30.8)
Noncarrier	30/282 (10.6)	55/291 (18.9)
Severe ARIA-H		
APOE ε4 homozygous carriers	3/174 (1.7)	41/168 (24.4)
APOE ε4 heterozygous carriers	1/538 (0.2)	48/522 (9.2)
Noncarrier	2/282 (0.7)	13/291 (4.5)
Serious ARIA-H[a]		
APOE ε4 homozygous carriers	0	2/168 (1.2)
APOE ε4 heterozygous carriers	0	1/522 (0.2)
Noncarrier	0	1/291 (0.3)

Abbreviations: APOE ε4 = allele subtype 4 of the gene coding for apolipoprotein class E; ARIA-H = amyloid-related imaging abnormalities–hemorrhage/hemosiderin deposition; Dona = donanemab; MRI = magnetic resonance imaging; n = number of patients within each specified category; n1 = number of patients in the analysis population; PC = placebo controlled.

[a] Based on MRI or TEAE cluster

Radiographic severity of ARIA-H in donanemab-treated patients was mostly mild (15%) or severe (10%) compared to mostly mild (10%) or moderate (2%) for placebo-treated patients. Isolated ARIA-H was mostly mild and was observed at a similar frequency for donanemab- and placebo-treated patients.

ARIA-H SAEs were reported for 4 (0.4%) donanemab-treated patients, 3 of which were concurrent with an SAE of ARIA-E.

One death due to ARIA-H was reported (Case 1 Dona-PC) with another death in a participant with serious ARIA-H and ARIA-E (Case 6 Dona-PC, already discussed in ARIA-E section) (Figure 6.11). These cases are discussed in Section 6.2.4.5, with further details available in Appendix 9.1.

Symptoms of ARIA-H were not systematically collected due to frequent co-occurrence with ARIA-E. The estimated frequency of symptomatic ARIA-H was 1.0% in the donanemab treatment group and 0.3% in the placebo group.

As with ARIA-E, the majority of ARIA-H radiographic events occurred by Week 24 and were managed by temporary or permanent discontinuation with and without the use of supportive treatment.

In the donanemab treatment group, 12% of patients had more than 1 ARIA-H event observed during the placebo-controlled period. Generally, after the first episode, recurrent ARIA-H in these patients was noted more frequently in the radiographically severe category for each subsequent episode.

Results from All Dona analyses evaluating ARIA-H were consistent with those observed in Dona-PC.

6.2.4.6.4. Intracerebral Hemorrhage Greater than 1 cm

In Dona-PC intracerebral hemorrhage greater than 1 cm frequency was similar at 0.3% of donanemab-treated patients compared with 0.2% of placebo-treated patients. Heterozygote APOE ε4 carriers had the highest frequency (donanemab, 0.6%). SAEs of intracerebral hemorrhage greater than 1 cm were uncommon in 1 (0.1%) donanemab-treated patient and 1 (0.1%) placebo-treated patient.

Results from All Dona analyses evaluating intracerebral hemorrhage greater than 1 cm were consistent with those observed in Dona-PC.

6.2.4.6.5. ARIA Events and Antithrombotic Use

More than 40% of patients in both treatment groups used concomitant antithrombotics. Aspirin was the most frequently used (greater than 30%) antithrombotic followed by anticoagulants (10%; heparins, warfarin, and direct oral anticoagulants).

When compared within treatment for both donanemab- and placebo-treated patients, the observed frequency of ARIA-E or ARIA-H in patients using antithrombotic medications (at any time or within 30 days prior to the event) and those not using antithrombotic medications was similar (Table 6.23).

The findings were similar for concomitant use/nonuse of aspirin, nonaspirin antiplatelets, or anticoagulants within both treatment groups.

Analysis for patients with concomitant use of thrombolytics and donanemab treatment is limited by the low numbers of patients in the placebo-controlled studies using these medications. There was 1 fatal case of donanemab and thrombolytic use in the All Dona analysis set (Case 32 All Dona, Appendix 9.1).

Table 6.23. Frequency of ARIA and Intracerebral Hemorrhage Greater than 1 cm Antithrombotic Medication Use, Based on MRI, Dona-PC, End of Treatment Period Plus 57 Days

	Dona-PC N = 1983	
	07 June 2023	
	Placebo N = 999 n/n1 (%)	Donanemab N = 984 n/n1 (%)
ARIA-E		
At least 1 antithrombotic used	8/431 (1.9)	93/413 (22.5)
Within 30 days prior to ARIA event[a]	7/431 (1.6)	87/413 (21.1)
Aspirin used	7/343 (2.0)	75/334 (22.5)
Nonaspirin antiplatelet used	0/40	11/58 (19.0)
Anticoagulant used	1/105 (1.0)	20/98 (20.4)
Thrombolytic used	0/2	0/1
No antithrombotic used	10/568 (1.8)	144/571 (25.2)
ARIA-H		
At least 1 antithrombotic used	56/431 (13.0)	137/413 (33.2)
Within 30 days prior to ARIA event[a]	55/431 (12.8)	125/413 (30.3)
Aspirin used	47/343 (13.7)	117/334 (35.0)
Nonaspirin antiplatelet used	8/40 (20.0)	16/58 (27.6)
Anticoagulant used	14/105 (13.3)	28/98 (28.6)
Thrombolytic used	0/2	0/1
No antithrombotic used	68/568 (12.0)	171/571 (29.9)
Intracerebral hemorrhage >1 cm		
At least 1 antithrombotic used	0/431	1/413 (0.2)
Within 30 days prior to ARIA event[a]	0/431	1/413 (0.2)
Aspirin used	0/343	0/334
Nonaspirin antiplatelet used	0/40	1/58 (1.7)
Anticoagulant used	0/105	0/98
Thrombolytic used	0/2	0/1
No antithrombotic used	2/568 (0.4)	2/571 (0.4)

Abbreviations: ARIA = amyloid-related imaging abnormalities; ARIA-E = amyloid-related imaging abnormalities–edema/effusions; ARIA-H = amyloid-related imaging abnormalities–hemorrhage/hemosiderin deposition; Dona = donanemab; n = number of patients within each specified category; n1 = number of patients in the analysis population; PC = placebo controlled.

[a] For participants who experienced multiple ARIA events, at least one ARIA event had antithrombotic use within 30 days prior to the event.

Results for All Dona with the use of concomitant antithrombotic medications are similar to those observed for the donanemab-treated patients in the Dona-PC analysis set.

One death due to intracranial hemorrhage was reported in a patient in Study AACI-LTE. The patient was treated with a thrombolytic medication for acute ischemic stroke (Case 32 All Dona, Appendix 9.1).

6.2.4.6.6. Risk Factors for ARIA

The risk of ARIA was evaluated using a number of intrinsic and extrinsic factors including the concomitant use of antithrombotic medications. The presence of APOE ε4 alleles is a known risk factor for ARIA and was evidenced in the observed frequency of ARIA-E/H in donanemab-treated patients, being the highest in homozygote APOE ε4 carriers, followed by heterozygote APOE ε4 carriers, as compared with noncarriers. This was also true for severe, serious, and symptomatic ARIA, where the frequencies of ARIA were highest in donanemab-treated homozygote APOE ε4 carriers. In addition, preexisting ARIA-H microhemorrhages and superficial siderosis were associated with a higher frequency of ARIA. The increased risk of ARIA-E based on APOE ε4 carrier status, baseline microhemorrhages, and superficial siderosis was reconfirmed using PK/PD modeling and post hoc ARIA risk factor analysis using logistic regression (Figure 9.9).

6.2.4.6.7. ARIA Management

Titration

Data obtained from Study AACI, prior to the introduction of dose titration (Amendment a), support that dose titration reduces the frequency of serious ARIA-E. In the Study AACI safety population, 43 patients received 1400 mg of donanemab as first dose, and 810 had dose titration. In patients without dose titration, the observed frequency of serious ARIA-E was 4.7%. By comparison, the frequency of serious ARIA-E in the patients with dose titration was 1.4%. It was also noted that the frequency of serious ARIA-E observed in the Phase 2 Study AACG (that applied dose titration) was also lower at 1.5%. Taken together and recognizing the limited number in the group without titration, it is observed that titration reduced the frequency of serious ARIA-E and supports the rationale for which the amendment was introduced.

Addition of Week 4 MRI

The majority of serious ARIA occurred in the first 12 weeks of treatment (Section 6.2.4.6.1). Further, analysis of ARIA SAEs in Study AACI shows that in 12 of the 14 events (excluding a case of ARIA-E and a case of ARIA-E and ARIA-H), the serious event occurred prior to the implementation of a protocol amendment to introduce a Week 4 MRI. Note that none of the 3 fatal events related to ARIA underwent a 4-week MRI. A review of data evaluating the effectiveness of the 4-week MRI showed that this MRI was associated with an approximate 25% decrease in the risk of serious ARIA and an approximate 35% decrease in the risk of symptomatic ARIA-E. While this analysis is limited by the low number of serious ARIA events, altogether this highlights the importance of the required Week 4 MRI as a risk minimization measure, which is reiterated in the proposed labeling.

Corticosteroids

Symptomatic or serious ARIA may benefit from treatment with corticosteroids. In donanemab studies, 8% of patients with first ARIA-E received supportive therapy, and 90% of those receiving supportive therapy was for events of symptomatic ARIA. The most frequently used steroids for supportive therapy were dexamethasone and/or prednisolone. Multiple studies report

efficacy of corticosteroid treatment in improving clinical and radiographic outcomes associated with cerebral amyloid angiopathy, which has related pathophysiological mechanisms to ARIA (Regenhardt et al. 2020; Antolini et al. 2021). Furthermore, current appropriate use guidelines also recommend early treatment initiation of high-dose steroids in management of serious and severe ARIA (Cummings et al. 2022, 2023).

Recommendations

Based on the learnings about ARIA, including the 3 fatal ARIA-related cases from the clinical trials, recommendations for managing ARIA include the following:

- Labeling identifying patients at increased risk for ARIA, including testing for APOE ε4 status as well as those with baseline MRI findings consistent with cerebral amyloid angiopathy.
- Dose titration as part of standard dose posology
- Monitoring MRI scans early in treatment with assessments prior to the second, third, fourth, and seventh infusion and for any symptomatic ARIA. Of note, the scan prior to the third infusion is proposed to be added to labeling after review of Study AACI data further clarified typical onset of serious ARIA.
- Dose interruption for radiographically moderate or severe, symptomatic or serious ARIA, and reassessment of benefit-risk
    - resume dosing after resolution or stability of MRI and symptoms (if present), or
    - permanent discontinuation of donanemab.
- Use of corticosteroids as appropriate for serious or symptomatic ARIA.

In addition, a health care professional educational program related to ARIA identification and management will be available. A patient card will also be offered to patients/caregivers that includes ARIA-related information and emergency contact details of the treating physician as well as patient details to inform and aid in managing any emergency situation.

Study AACI-LTE is ongoing and will provide longer-term safety data for the use of donanemab beyond 18 months in those that had not cleared amyloid plaque. As of 14 April 2023, a total of 300 patients have received 18 or more and 30 patients have received 24 or more donanemab infusions, per treatment regimen.

Post-authorization safety studies are also planned to further characterize safety risks, including ARIA and IRRs (Section 7).

6.2.4.7. Infusion-Related Reactions

IRRs were commonly observed in the donanemab-treated patients (8.5%). Most were mild to moderate in severity (94%) and occurred during infusion or within 30 minutes postinfusion. The most common signs and symptoms of IRRs were erythema, nausea or vomiting, chills, and sweating. The majority of IRRs were transient and resolved on the same day (median 0.5 days, mean 0.7 days).

Three (0.3%) donanemab-treated patients had anaphylactic reactions reported and all were nonserious.

Some events of hypersensitivity were reported and based on review, these events also occurred during or within 30 minutes and had clinical signs consistent with the reported IRRs.

The following immediate hypersensitivity events were reported in more than 1 donanemab-treated patient:

- IRR: n = 82 (8.3%)
- hypersensitivity: n = 10 (1.0%)
- anaphylactic reaction: n = 3 (0.3%), and
- urticaria: n = 2 (0.2%).

In All Dona, immediate hypersensitivity events occurred in 9.3% of patients with the majority due to IRRs (8.0%). Serious IRR or hypersensitivity was uncommonly reported (0.6%) and included 5 SAEs of anaphylaxis (0.2%). None of the events were fatal. Anaphylactic reaction has been included as an ADR for donanemab in the proposed labeling.

Among donanemab-treated patients, the majority of first-onset IRRs occurred by the fourth infusion, and all serious hypersensitivity or IRR events occurred by the fourth infusion.

6.2.4.7.1. Infusion-Related Reaction Management

IRR was managed by close monitoring during and for at least 30 minutes after each infusion, and slowing the infusion and/or providing supportive therapy based on clinical presentation. Most IRR events (approximately 67%) did not require any supportive therapy. When supportive therapy was used, it was most often diphenhydramine or paracetamol.

Irrespective of slowing of infusion, prophylaxis medication, or supportive therapy, most IRRs were mild or moderate in severity, transient, and resolved on the same day.

On subsequent infusions, around 40% of patients had an IRR whether they received prophylaxis or slowed the infusion on rechallenge and 60% did not have an IRR.

A slower infusion or use of prophylaxis did not reduce the chance of an IRR upon rechallenge.

Recommendations

Serious hypersensitivity can be managed through warning language in labeling, monitoring during infusion, and observing for at least 30 minutes postinfusion, providing symptomatic therapy when needed. Contraindications should be followed to ensure patients with known serious hypersensitivity to donanemab or excipients do not initiate donanemab treatment.

6.2.4.8. Immunogenicity

In clinical studies, 88% of donanemab-treated patients developed ADA and all of the patients with ADA had neutralizing antibodies. Although donanemab exposure decreased with increasing ADA titer, the development of ADA was not associated with the loss of clinical efficacy of donanemab. All patients reporting IRRs had ADA. Higher ADA titer was associated with an

increased incidence of IRRs/immediate hypersensitivity events. The majority of patients in the high titer group did not have IRRs.

6.2.4.9. Additional Safety Topics

6.2.4.9.1. Vital Signs, Physical Findings, and Hepatic Safety Observations

No clinically meaningful findings were observed in the clinical laboratory values, vital signs, and electrocardiogram data. Regarding hepatic safety, no imbalance was observed between donanemab- and placebo-treated groups in the frequency of hepatic enzyme changes or shifts above the upper limit of normal. No imbalance was observed in the frequency of reported hepatic AEs, and events in donanemab-treated patients were transient with no trends or patterns in the type of event or time to onset. The totality of the data does not support an association of hepatic safety concerns with donanemab.

6.2.4.9.2. Suicidal Ideation

Thirty-eight patients in the donanemab group (n = 38, 3.9%) reported any of the 5 suicidal ideation C-SSRS scores (1 to 5) during treatment, compared with the placebo group (n = 45, 4.5%). No reports of suicidal behavior at baseline or during treatment in the donanemab group compared with the placebo group (n = 2, 0.2%) were noted.

In Dona-PC, 2 SAEs of suicidal ideation and behavior were reported in the donanemab group and 2 SAEs in the placebo group. In All Dona, an additional 2 SAEs were reported in the donanemab group. Of these SAEs, 3 were fatal; 2 in the donanemab group and 1 in the placebo group (Appendix 9.1).

Based on the results of the C-SSRS and reported AEs, no increased risk of suicide was noted with donanemab treatment.

6.2.4.9.3. Safety in Special Groups and Situations

No clinical studies of donanemab in pregnant or breastfeeding women were conducted, these patients were excluded from the clinical trials and no animal studies were conducted to assess the potential reproductive or developmental toxicity of donanemab (consistent with regulatory guidance for mAb). No cases of donanemab overdose have been reported, and no findings that donanemab causes physical or psychological dependency.

Adverse events in subgroups

No clinically meaningful interactions by age, race, sex, ethnicity, or baseline tau (low-medium versus high) were observed between treatment groups in Dona-PC on the frequency of common TEAEs. An evaluation of the safety profile between the no-very low tau group in the separate Addendum, the low-medium tau group from Study AACI, and the high-tau population from Study AACI is shown in Table 6.24. In general, aside from a lower frequency of ARIA-E and ARIA-H in the no-very low tau subgroup, safety profile based on tau pathology was similar across no- very low tau, low-medium, and high-tau-only populations.

6.2.4.10. Comparison of Safety Based on Tau Pathology

In general, aside from a lower frequency of ARIA-E and ARIA-H in the no-very low tau subgroup, safety profile based on tau pathology was similar across no-very low tau, low-medium, and high-tau-only populations. Regarding mortality, no trend or pattern was noted in the types of events that were fatal, and no association based on tau pathology was noted (Table 6.25).

Table 6.24. Overview of AE across the Tau Pathology Spectrum

	Addendum No-Very Low Tau Subpopulation	AACI Low-Medium Tau Population	AACI High Tau Subpopulation
	08 August 2023	14 April 2023	14 April 2023
	Donanemab (N = 250) n (%)	Donanemab (N = 584) n (%)	Donanemab (N = 268) n (%)
Overview of AE			
Deaths	5 (2.0)	12 (2.1)	4 (1.5)
SAEs	45 (18.0)	97 (16.6)	51 (19.0)
DCAE (study)	16 (6.4)	50 (8.6)	19 (7.1)
DCAE (study treatment)	23 (9.2)	82 (14.0)	30 (11.2)
TEAEs	215 (86.0)	522 (89.4)	237 (88.4)
Overview of ARIA[a]			
Any ARIA	70 (28.0)	211 (36.1)	103 (38.4)
ARIA-E	43 (17.2)	138 (23.6)	67 (25.0)
Symptomatic	9 (3.6)	36 (6.2)	16 (6.0)
ARIA-H	60 (24.0)	179 (30.7)	89 (33.2)
Intracerebral hemorrhage >1 cm	2 (0.8)	3 (0.5)	0
Infusion-related reaction[b]	18 (7.2)	53 (9.1)	21 (7.8)

Abbreviations: AACI = I5T-MC-AACI; AE = adverse event; ARIA = amyloid-related imaging abnormalities; ARIA-E = amyloid-related imaging abnormalities–edema/effusions; ARIA-H = amyloid-related imaging abnormalities–hemorrhage/hemosiderin deposition; DCAE = discontinuation of study treatment due to an adverse event; MRI = magnetic resonance imaging; N = number of patients in the analysis population; n = number of patients within each specified category; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

[a] Based on MRI or TEAE cluster.

[b] Preferred term.

Sources: AACI.8.248, AACI.8.249, AACI.8.252, AACI.8.254 low-medium and high, Sims et al. 2023; JAMA Supplement 3

Table 6.25. Comparison of Mortality Based on Tau Pathology

	Addendum No-Very Low Tau Subpopulation	AACI Low-Medium Tau Population	AACI High-Tau Subpopulation
	08 August 2023	07 June 2023	07 June 2023
	Donanemab (N = 250) n (%)	Donanemab N = 584 n (%)	Donanemab (N = 268) n (%)
Overview of mortality			
Total deaths	5 (2.0)	12 (2.1)	5 (1.9)
Death	1 (0.4)	2 (0.3)	1 (0.4)
Completed suicide	0	1 (0.2)	1 (0.4)
Pulmonary embolism	0	1 (0.2)	1 (0.4)
ARIA-H	0	1 (0.2)	0
ARIA-E	0	1 (0.2)	0
Cerebrovascular accident	0	0	1 (0.4)
COVID-19	0	1 (0.2)	0
COVID-19 pneumonia	0	1 (0.2)	0
Dehydration	0	0	1 (0.4)
Dementia Alzheimer's type	0	1 (0.2)	0
Gun shot wound	1 (0.4)	0	0
Head injury	1 (0.4)	0	0
Pancreatic carcinoma metastatic	1 (0.4)	0	0
Pelvic fracture	1 (0.4)	0	0
Pneumonia bacterial	1 (0.4)	0	0
Respiratory arrest	0	1 (0.2)	0
Retroperitoneal hemorrhage	0	1 (0.2)	0
Subarachnoid hemorrhage	0	1 (0.2)	0

Abbreviations: AACI = I5T-MC-AACI; ARIA-E = amyloid-related imaging abnormalities–edema/effusions; ARIA-H = amyloid-related imaging abnormalities–hemorrhage/hemosiderin deposition; COVID-19 = coronavirus disease 2019; MedDRA = Medical Dictionary for Regulatory Activities; n = number of patients with at least 1 adverse event with fatal outcome; N = number of patients in the analysis population.

MedDRA Version 25.1.

7. RISK MANAGEMENT AND PROPOSED POST-AUTHORIZATION STUDIES

See Section 6.2.4.6.7 for information on management for ARIA and Section 6.2.4.7.1 for information on management for IRRs.

Safety concerns identified through the donanemab clinical trial program can be managed through proper labeling, and can be further studied post-approval. Post-authorization studies and surveillance activities are a critical part of further characterizing the safety of a drug, particularly for uncommon to rare AEs. Drugs are approved on the basis of clinical trials, which involve relatively small numbers of people who have been explicitly selected for this purpose. Despite the largest registration safety database for an amyloid-targeting therapy, further characterization of uncommon to rare safety events cannot be accomplished within the limitations of the donanemab clinical trial program and is best suited for the larger postmarketing population. Post-authorization studies offer further characterization of the safety profile of a drug in the broader and more diverse AD population including patients who have a wide variety of medical conditions. Lilly has proposed 3 post-authorization safety studies to address the key risks of donanemab, specifically, serious hypersensitivity reactions, ARIA-E and ARIA-H, and intracerebral hemorrhage greater than 1 cm with the use of antithrombotic medications. These 3 studies are outlined below.

Study 1: Site-based observational study to characterize ARIA within a cohort of donanemab-treated patients

This is a site-based single-arm observational registry study. The study will be executed within a US cohort of donanemab users with primary data collected in collaboration with the patients' treating health care professional as part of routine clinical practice.

The study objectives will characterize (1) asymptomatic and symptomatic ARIA-E and ARIA-H, (2) incidence of intracerebral hemorrhage greater than 1 cm with the use of antithrombotics, and (3) serious hypersensitivity. ARIA-E and ARIA-H will be assessed based on MRIs received in routine clinical practice and ARIA-related symptoms will be described. Patients with ARIA will be followed to document real-world interventions and ARIA resolution/stabilization. Additional patient characterization will include a description of baseline demographics, comorbidities, and comedications (including the use of antithrombotic medications).

Study 2: Study to characterize safety and drug utilization in donanemab-treated US patients

This is an observational single-arm cohort study conducted within cohorts of US donanemab users treated in routine clinical care using US claims data (for example, Medicare claims, commercial claims, and Medicaid claims). The objectives are to characterize (1) the incidence of serious hypersensitivity reactions in patients with AD treated with donanemab and (2) the incidence of intracerebral hemorrhage in patients with AD treated with donanemab who are also using antithrombotic medication. In addition, characteristics of donanemab users including the proportion of patients that concomitantly use antithrombotic medications and the proportion of patients with both AD and Down syndrome will be assessed.

Study 3: Study to characterize safety and drug utilization in donanemab-treated European patients

This is an observational single-arm cohort study conducted within cohorts of European donanemab users treated in routine clinical care using 3 to 4 European secondary databases (for example, claims and electronic medical records). The objectives of this study are similar to Study 2 above and include characterization of (1) the incidence of serious hypersensitivity reactions in patients with AD treated with donanemab and (2) the incidence of intracerebral hemorrhage in patients with AD treated with donanemab who are also using antithrombotic medication. This study will also assess characteristics of donanemab users including the proportion of patients that concomitantly use antithrombotic medications and the proportion of patients with both AD and Down syndrome will be assessed.

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9. APPENDICES

9.1. Death Narrativesfrom Pre-specified Analysis

Individual reports of mortality were reviewed for possible association with donanemab treatment. Three of the deaths reported in the donanemab population in Dona PC were related to donanemab treatment. Specifically, 2 were reported as ARIA (1 ARIA-E and 1 ARIA-H and 1 event reported as "Death" occurred in a patient with ongoing serious ARIA-E and ARIA-H.

Table 9.1. Adverse Event Leading to Death, Incidence Adjusted for Observation Time, Donanemab Placebo-Controlled Analysis Sets, End of Treatment Period Plus 57 Days

	AACI N = 1727		Dona-PC N = 1983	
Data Cutoff Date	**07 June 2023**		**07 June 2023**	
System Organ Class Preferred Term	**Placebo N = 874 PYO = 1237.4 n (%) [IR]**	**Donanemab N = 853 PYO = 1172.3 n (%) [IR]**	**Placebo N = 999 PYO = 1420.1 n (%) [IR]**	**Donanemab N = 984 PYO = 1357.0 n (%) [IR]**
Subjects with ≥1 Fatal AE	10 (1.1) [0.8]	17 (2.0) [1.5]	12 (1.2) [0.8]	18 (1.8) [1.3]
Cardiac disorders	1 (0.1) [0.1]	0	2 (0.2) [0.1]	0
Cardiac arrest			1 (0.1)	0
Myocardial infarction	1 (0.1)	0	1 (0.1)	0
Gastrointestinal disorders	0	1 (0.1) [0.1]	0	1 (0.1) [0.1]
Retroperitoneal hemorrhage	0	1 (0.1)	0	1 (0.1)
Nervous system disorders	1 (0.1) [0.1]	5 (0.6) [0.4]	1 (0.1) [0.1]	5 (0.5) [0.4]
ARIA-E	0	1 (0.1)	0	1 (0.1)
ARIA-H	0	1 (0.1)	0	1 (0.1)
Cerebrovascular accident	0	1 (0.1)	0	1 (0.1)
Dementia Alzheimer's type	1 (0.1)	1 (0.1)	1 (0.1)	1 (0.1)
Subarachnoid hemorrhage	0	1 (0.1)	0	1 (0.1)
General disorders and administration site conditions	1 (0.1) [0.1]	3 (0.4) [0.3]	1 (0.1) [0.1]	3 (0.3) [0.2]
Death	1 (0.1)	3 (0.4)[a]	1 (0.1)	3 (0.3)[a]
Infections and infestations	3 (0.3) [0.2]	2 (0.2) [0.2]	4 (0.4) [0.3]	3 (0.3) [0.2]
COVID-19	0	1 (0.1)	0	1 (0.1)
COVID-19 pneumonia	0	1 (0.1)	0	1 (0.1)
Pneumonia	2 (0.2)	0	2 (0.2)	1 (0.1)
Pneumonia aspiration			1 (0.1)	0
Sepsis	1 (0.1)	0	1 (0.1)	0
Injury, poisoning, and procedural complications	1 (0.1) [0.1]	0	1 (0.1) [0.1]	0
Respiratory fume inhalation disorder	1 (0.1)	0	1 (0.1)	0
Metabolism and nutrition disorders	0	1 (0.1) [0.1]	0	1 (0.1) [0.1]

	AACI N = 1727		Dona-PC N = 1983	
Data Cutoff Date	**07 June 2023**		**07 June 2023**	
System Organ Class Preferred Term	**Placebo N = 874 PYO = 1237.4 n (%) [IR]**	**Donanemab N = 853 PYO = 1172.3 n (%) [IR]**	**Placebo N = 999 PYO = 1420.1 n (%) [IR]**	**Donanemab N = 984 PYO = 1357.0 n (%) [IR]**
Dehydration	0	1 (0.1)	0	1 (0.1)
Psychiatric disorders	1 (0.1) [0.1]	2 (0.2) [0.2]	1 (0.1) [0.1]	2 (0.2) [0.1]
Completed suicide	1 (0.1)	2 (0.2)	1 (0.1)	2 (0.2)
Respiratory, thoracic, and mediastinal disorders	1 (0.1) [0.1]	3 (0.4) [0.3]	1 (0.1) [0.1]	3 (0.3) [0.2]
Pulmonary embolism	0	2 (0.2)	0	2 (0.2)
Respiratory arrest	0	1 (0.1)	0	1 (0.1)
Respiratory failure	1 (0.1)	0	1 (0.1)	0
Vascular disorders	1 (0.1) [0.1]	0	1 (0.1) [0.1]	0
Arteriosclerosis	1 (0.1)	0	1 (0.1)	0

Abbreviations: AACI = I5T-MC-AACI; AE = adverse event; ARIA-E = amyloid-related imaging abnormalities–edema/effusions; ARIA-H = amyloid-related imaging abnormalities–hemorrhage/hemosiderin deposition; CI = confidence interval; COVID-19 = coronavirus disease 2019; IR = incidence rate; LTE = long-term extension; n = number of patients within the particular category adverse event; N = number of patients in the analysis population; PC = placebo controlled; SAE = serious adverse event.

[a] Includes the additional participant who died with ongoing SAE of ARIA-E.
Note: Patients are followed from the first dose of treatment to the end of treatment period +57 days, or the day prior to the first LTE visit, whichever occurs first.

Further review of the individual events from the pre-specified analysis and from Dona-PC showed

- 3 other nonrelated events in the donanemab-treated patients in the Nervous system disorders system organ class
  - 1 cerebrovascular accident in a patient after a carotid endarterectomy
  - 1 subarachnoid hemorrhage after a fall in a patient who was randomly assigned to donanemab and had received 2 infusions of saline after meeting amyloid clearance in Dona-PC, and
  - 1 event of AD after multiple SAEs of erosive gastritis and esophagitis
- 3 events in the General disorders and administration site conditions
  - 1 associated with ARIA already discussed above
  - 1 patient who died in her sleep with a previous nonserious AE of peripheral edema, and
  - 1 patient who died 12 days after multiple fractures from a presumed fall from bed
- 2 donanemab-treated patients died from a pulmonary embolism where each had multiple risk factors
- 2 suicides in the donanemab group compared with 1 patient in the placebo group, and
- all other deaths were a single type of event in patients with risk factors.

An evaluation of risk factors for death from the donanemab-treated patients in Dona-PC and All Dona showed the causes of death appeared to be primarily explained by patient age, disease progression, comorbidities in patient medical history, and/or the use of confounding concomitant medications. Most were a single type of event, each presenting with multiple risk factors. In Dona-PC, beyond the 3 deaths associated with ARIA, the other events leading to higher number of deaths in the donanemab group had no discernible pattern or trend in the type of event, timing, frequency, or nature of the events that led to death, and all were assessed not related to donanemab by the study investigator.

Table 9.2. Case Summaries for Adverse Events Leading to Death Occurring in Dona-PC, Pre-specified Analysis

Case Number	Fatal Event	Day of Death	Demographics	Relevant Information	Days since Last Dose to Death
Donanemab-treated patients, n = 18					
1	Amyloid-related imaging abnormalities–microhemorrhages and hemosiderin deposits	75	73, White, male	HTN, hypercholesterolemia, APOE ε4 noncarrier, baseline superficial siderosis (50 mm)	46
2	ARIA-E	80	73, White, female	MRI normal at screening, APOE ε4 heterozygote	24
3	Cerebrovascular accident	584	76, White, female	Carotid endarterectomy complication	139
4	Dementia Alzheimer's type	154	84, White, female	GERD, SAEs of erosive gastritis, esophagitis, hypertensive emergency, previous MI	56
5	Subarachnoid hemorrhage	244	84, White, male	Hx of HTN and fall. Fall on SD 237 with vertebral fracture.	82
6	Death	447	76, White, male	SAEs of ARIA on rechallenge, APOE ε4 heterozygote	48
7	Death	63	83, White, female	HTN, osteopenia, hyperlipidemia, basal cell carcinoma, and mild peripheral edema (SD 41); patient died during sleep.	34
8	Death	536	83, White, female	HTN, DM, left hip fractures, and replacement SAE of multiple fracture on SD 524	37
9	COVID-19	352	80, White, male	AFIB, HTN, cardiomegaly, COPD	15
10	COVID-19 pneumonia	85	82, White, male	HTN, T2DM asthma, nephropathy	30
11	Pneumonia	36	85, White, female	Coronary artery bypass, TIA, nephropathy, HTN	5
12	Retroperitoneal hemorrhage	273	82, White, female	HTN, MI, pHTN, cardiac valve disease, and failure	18
13	Dehydration	81	68, White, male	HTN, T2DM, pneumonia, visual hallucinations	58
14	Pulmonary embolism	3	69, White, female	AFIB, mitral valve prolapse, HTN, lung disorder, T2DM, sleep apnea, hereditary spherocytosis	2
15	Pulmonary embolism	215	81, White, female	Smoker, concomitant raloxifene (PE in label)	74
16	Respiratory arrest	331	73, White, male	Dyslipidemia, DM, carotid artery disease and stenosis, alcohol use	50
17	Completed suicide	175	62, White, male	Paranoia/delusions hypothyroidism and circadian rhythm sleep disorder, sleep apnea	35
18	Completed suicide	314	77, White, male	Ongoing depression	5

Case Number	Fatal Event	Day of Death	Demographics	Relevant Information	Days since Last Dose to Death
Placebo-treated patients, n = 12					
19	Dementia Alzheimer's type	520	79, White, male	Dementia, cerebral atrophy, HTN, sports injury, and work injury	8
20	Death	265	85, White, male	History of bilateral knee replacement, spinal surgery, and prolonged hospitalization due to lower limb fracture	67
21	Cardiac arrest	99	79, White, female	Found unresponsive, was not revived	9
22	Myocardial infarction	254	75, White, female	Angina, HTN, TIA, CAD.	23
23	Pneumonia aspiration	558	79, White, male	COVID-19 with systolic murmur, peripheral arterial occlusive disease, HTN, dyslipidemia	212
24	Pneumonia	139	82, White, male	History of smoking, HTN, tachycardia, with SAEs of AFIB, pneumonia, sepsis	82
25	Pneumonia	147	86, White, female	History of HTN, CKD-developed lethargy, weakness, hypoxia	146
26	Sepsis	291	83, White, male	History of prostate cancer and radiation with SAEs of obstructive pancreatitis, bile stones, aspiration pneumonia, GI bleeding and sepsis	67
27	Respiratory failure	28	85, White, male	T2DM, obesity with SAE of COVID-19	27
28	Completed suicide, carbon monoxide poisoning	277	79, White, male	History of depression with treatment, no affirmative response on C-SSRS	24
29	Respiratory fume inhalation disorder	176	84, White, female	Smoke inhalation secondary to house fire from natural disaster	14
30	Arteriosclerosis	351	66, White, female	Hypercholesteremia, T1DM, no prior symptoms	10

Abbreviations: AFIB = atrial fibrillation; APOE ε4 = allele subtype 4 of the gene coding for apolipoprotein class E; ARIA = amyloid-related imaging abnormalities; CAD = coronary artery disease; CKD = chronic kidney disease; COPD = chronic obstructive pulmonary disease; COVID-19 = coronavirus disease 2019; C-SSRS = Columbia-Suicide Severity Rating Scale; DM = diabetes mellitus; GERD = gastroesophageal reflux disease; GI = gastrointestinal; HTN = hypertension; Hx = history; MI = myocardial ischemia; MRI = magnetic resonance imaging; n = number of patients; PC = placebo controlled; PE = pulmonary embolism; pHTN = pulmonary hypertension; SAE = serious adverse event; SD = study day; T1DM = type 1 diabetes; T2DM = type 2 diabetes mellitus; TIA = transient ischemic attack.

9.1.1. Dona-PC: Donanemab-Treated Patients

9.1.1.1. Nervous System Disorders

Case 1 Dona-PC (Amyloid-related imaging abnormalities-microhemorrhages and hemosiderin deposits; donanemab)

A 73-year-old White male (APOE ε4 noncarrier) with hypertension and hypercholesterolemia had superficial siderosis (50 mm) in the left frontal lobe on baseline MRI. The second dose of donanemab 700 mg was on SD 29. On SD 46, headache with mild ARIA-E was reported and donanemab was not restarted. MRI on SD 71 showed mild ARIA-E in left parietal, right occipital, and right temporal lobes, with 1 microhemorrhage and 4 areas of superficial siderosis. On SD 72, the patient developed right hemiplegia and aphasia, and brain CT scan showed a large left posterior parietal hematoma (55 mm x 43 mm). Several acetylsalicylic acid tablets had reportedly been given that morning, amount unknown. The patient died on SD 75 with hemorrhagic stroke and ARIA-H assessed as related to donanemab.

- *Considerations include presence of large superficial siderosis as a baseline risk for ARIA-H and possible contribution of acetylsalicylic acid on the clinical course of the event.*

Case 2 Dona-PC (Amyloid-related imaging abnormalities–edema; donanemab)

A 73-year-old White female (APOE ε4 heterozygote) with low-medium baseline tau had normal screening MRI was started on donanemab treatment with the last dose (third 700 mg dose) on SD 56. The patient presented with symptoms of confusion, agitation, forgetfulness, short attention span, garbled speech, and disorientation with an SAE of ARIA-E on SD 66. On SD 72, head CT scan showed a sliver of hyperdensity within the right posterior and anterior frontal lobe sulci along the vertex, possible new foci of subarachnoid hemorrhage, and extensive vasogenic edema throughout the right cerebral hemisphere and some within the left occipital lobe. On SD 75, the patient was discharged to hospice care and died on SD 80. The event was assessed as related to the study drug.

- *Considerations: ARIA-E is causally associated with donanemab treatment and does not appear that supportive treatment was initiated.*

Case 3 Dona-PC (Cerebrovascular accident; donanemab)

A 76-year-old White female (APOE ε4 noncarrier) with medical history of hypercholesterolemia, atrial fibrillation, hypertension, carotid artery occlusion, coronary artery disease, peripheral vascular disorder, and neuropathy peripheral. The patient started to receive donanemab on SD 1 with last dose (17^{th} dose) on SD 445. On SD 465, the patient was hospitalized for carotid endarterectomy with an SAE of cerebrovascular accident (severe) reported on SD 466 with prolonged hospitalization. The patient died on SD 584. Study investigator reported that cerebral vascular accident was a likely complication of the carotid surgery.

- *Considerations: Patient had medical history of cerebrovascular risk factors of bilateral carotid artery occlusions, hypertension, hypercholesterolemia, atrial fibrillation, and advanced age. Postoperative cerebrovascular accident is a known complication of carotid endarterectomy.*

Case 4 Dona-PC (Dementia Alzheimer's type; donanemab)

An 84-year-old White female (APOE ε4 heterozygote) with medical history of gastroesophageal reflux disease, hyperlipidemia, hypertension, and depression. The patient started to receive donanemab on SD 1 with last dose of donanemab given on SD 98. Prior to the fatal event, the patient had presented with 2 events of esophagitis (SDs 103 and 137), 2 events of gastritis erosive (SDs 109 and 137), and acute myocardial infarction and hypertensive emergency (both on SD 106). Reportedly, the patient periodically refused medications and treatment over the course of hospitalizations, contributing to malnutrition and difficulty in managing symptoms. Due to poor prognosis and treatment noncompliance, the patient was discharged home on SD 143 with hospice care. On SD 154, the patient began experiencing trouble breathing, had an SAE of dementia Alzheimer's type (severe), and died. The investigator reported cause of death as late onset AD, which was unrelated to the study drug.

- *Considerations: Patient had multiple hospitalizations for MI, hypertensive emergency, esophagitis Grade IV, erosive gastritis, and malnutrition, and was frequently noncompliant; likely contributing to disease progression.*

Case 5 Dona-PC (Subarachnoid hemorrhage; donanemab)

An 84-year-old White male (APOE ε4 noncarrier) with history of fall, hypertension, and type 2 diabetes mellitus and receiving acetylsalicylic acid for coronary artery disease started donanemab with last dose on SD 162. On SD 237, the patient fell with thoracic vertebral fracture and subarachnoid hemorrhage. Platelets were administered for acetylsalicylic acid reversal, and the patient died on SD 244 due to subarachnoid hemorrhage. Per the investigator, the subarachnoid hemorrhage was not attributed to donanemab, as it could be trauma related and the patient had no ARIA detected in the previous MRI completed.

- *Considerations: Subarachnoid hemorrhage event include recent fall in a patient of advanced age with dementia and prior history of fall as risk factors.*

9.1.1.2. General Disorders and Administration Site Conditions

Case 6 Dona-PC (Death; donanemab)

A 76-year-old White male (APOE ε4 heterozygote) with low-medium baseline tau started donanemab. On SD 79, after 3 doses of donanemab 700 mg, MRI scan showed severe ARIA-E in the right frontal, occipital, parietal, and temporal lobes with 11 microhemorrhages and mild ARIA-H, both asymptomatic. Donanemab was interrupted due to ARIA-E and ARIA-H, with ARIA-H resolved on SD 167 and ARIA-E resolved on SD 195. On SD 202, donanemab was restarted, with symptomatic ARIA-E reported on SD 413. Symptoms were confusion and balance disorder. Last donanemab dose was on SD 399. The patient was hospitalized (SD 427) with SAEs of ARIA-E and ARIA-H and symptoms of nausea and vomiting. Dexamethasone was

initiated but the patient received only 1 day of treatment. On SD 428, the patient was discharged from the hospital, transferred to inpatient hospice, and died on SD 447. The investigator assessed the death as related to donanemab.

- *Considerations: This fatal event subsequent to serious events of ARIA-E and ARIA-H is considered related to donanemab. Patient was discharged to hospice by family and did not receive full course of steroid treatment.*

Case 7 Dona-PC (Death; donanemab)

An 83-year-old White female (APOE ε4 heterozygote) with medical history of hypertension, depression, osteopenia, hyperlipidemia, seronegative spondyloarthropathy, basal cell carcinoma, and squamous cell carcinoma of right forearm was started on donanemab treatment with last dose on SD 29. On SD 41, mild peripheral edema (nonserious) was reported with death on SD 63. Patient died during sleep, and no symptoms were reported prior to death. No cause of death was reported, and the event was assessed as unrelated to treatment.

- *Considerations: The previous nonserious adverse event of peripheral edema may indicate comorbid cardiovascular disease that was not reported and contributed to patient dying during sleep.*

Case 8 Dona-PC (Death; donanemab)

An 83-year-old White female (APOE ε4 heterozygote) with history of hypertension, diabetes mellitus, left hip replacement, and left hip fracture was started on donanemab treatment with last dose on SD 499. The patient was found on the floor with multiple fractures on SD 524, presumed due to a fall. Fall was presumed to be the cause of multiple fractures; however, the patient did not recall what happened. On SD 536, the patient died from natural causes. Patient reportedly went into cardiac arrest and cardiopulmonary resuscitation was attempted without success. The investigator assessed the SAEs of multiple fractures and death as not related to the study drug.

- *Considerations: Details of recent multiple fractures in a patient over 80 years of age is most likely contribution to the reported cardiac arrest.*

9.1.1.3. Infections and Infestations

Case 9 Dona-PC (COVID-19; donanemab)

An 80-year-old White male (APOE ε4 noncarrier) with medical history of atrial fibrillation, hypertension, cardiomegaly, and chronic obstructive pulmonary disease was started on donanemab treatment with last dose (13^{th}) on SD 337. On SD 346, the patient was hospitalized with SAE of COVID-19, and nonserious COVID-19 pneumonia and urinary tract infection. The patient's condition continued to decline, was transferred to hospice, and died on SD 352. Death certificate listed COVID-19 as the primary cause of death, and the event was assessed as unrelated to donanemab.

- *Considerations: Narrative indicates severe course of COVID-19 in an 80-year old patient with history of chronic obstructive pulmonary disease and cardiovascular risks*

(hypertension, atrial fibrillation, cardiomegaly); it is consistent with outcomes during the pandemic.

Case 10 Dona-PC (COVID-19 pneumonia; donanemab)

An 82-year-old White male (APOE ε4 heterozygote) with medical history of hypertension, type 2 diabetes mellitus, asthma, chronic obstructive pulmonary disease, obstructive sleep apnea, and cardiac failure was started on donanemab treatment with last dose on SD 55. On SD 70, the patient was hospitalized due to COVID-19 pneumonia, developed acute respiratory distress syndrome, non-ST-elevation myocardial infarction, new onset atrial fibrillation, acute kidney insufficiency, deep vein thrombosis; and decompensated rapidly requiring rapid sequence intubation. Treatment included etomidate, propofol, norepinephrine, fentanyl, remdesivir, insulin, alteplase, and heparin. On SD 85, the patient died due to COVID-19 pneumonia (SD 85), and the event was assessed as not related to the study drug.

- *Considerations: Complications reported in this severe case of COVID-19 pneumonia in patient more than 80 years of age with history of hypertension, type 2 diabetes mellitus, asthma, chronic obstructive pulmonary disease, sleep apnea, and cardiac failure are consistent with presentation of similar fatal cases during the pandemic.*

Case 11 Dona-PC (Pneumonia; donanemab)

An 85-year-old White female patient (APOE ε4 noncarrier) with medical history of coronary artery bypass, transient ischemic attack, hypertension, hypothyroidism, and gastroesophageal reflux disease was started on donanemab treatment with last dose on SD 31. On SD 35, patient was hospitalized for pneumonia with possible aspiration. Chest x-ray showed questionable early right lower lobe pneumonia; left lung was clear, and blood culture was negative. The patient's respiratory status worsened. On SD 36, the patient died. The event of pneumonia was assessed as unrelated to the study drug.

- *Considerations: Pneumonia is a common event in the elderly AD population and presence of right lower lobe pathology with clear left lung lobe involvement is consistent with aspiration as a causal factor.*

9.1.1.4. Gastrointestinal Disorders

Case 12 Dona-PC (Retroperitoneal hemorrhage; donanemab)

An 82-year-old White female (APOE ε4 noncarrier) with medical history of dyslipidemia, hypertension, myocardial ischemia, pulmonary hypertension, cardiac valve disease, and cardiac failure congestive and receiving warfarin as a concomitant medication was started on donanemab treatment with last dose on SD 255. On SD 267, the patient presented with retroperitoneal bleeding and was hospitalized. Despite multiple attempts to cauterize the area and supplementing with blood, patient's condition worsened due to complications, including renal failure. On SD 273, the patient died due to retroperitoneal bleeding. The investigator assessed the event as unrelated to the study drug and related to the concomitant medication, warfarin.

- *Considerations: Contribution to the retroperitoneal hemorrhage event included concomitant use of warfarin and renal failure. No plausible mechanism exists for a relationship with the study treatment.*

9.1.1.5. Metabolism and Nutrition Disorders

Case 13 Dona-PC (Dehydration; donanemab)

A 68-year-old White male (APOE ε4 homozygote) with history of visual hallucination related to AD was started on donanemab with last dose (second) on SD 23. Prior to the fatal event, the patient had hyponatremia (SD 42), paranoid delirium with psychotic elements (SD 43) requiring hospitalization, and dysphagia (SD 55). The patient had low-grade fever, urinary retention, and hematuria. Hyponatremia was associated with not eating and drinking properly. On SD 43, head CT scan and chest X-ray were normal, with MRI showing mild chronic microvascular ischemic changes on SD 46. Hospitalization was prolonged due to dehydration (severe), and the patient died (SD 81). Death certificate indicated cause of death was dehydration due to dysphagia and dementia, and the event was assessed as not related to the study drug.

- *Considerations: Hyponatremia, inappetence, and possible urinary tract infection contributing to dehydration along with preexisting dysphagia.*

9.1.1.6. Respiratory, Thoracic, and Mediastinal Disorders

Case 14 Dona-PC (Pulmonary embolism; donanemab)

A 69-year-old White female (APOE ε4 homozygote) with body mass index of 27.4 kg/m^2 and medical history of atrial fibrillation, mitral valve prolapse, hypertension, lung disorder, type 2 diabetes mellitus, sleep apnea syndrome, and hereditary spherocytosis was started on donanemab treatment. The patient did not complain about any symptoms or discomfort after the first dose. On SD 3, the patient died. In the autopsy report, cause of death was pulmonary embolism and patient's immobility from AD contributed to the fatal event. The investigator assessed the event of pulmonary embolism as unlikely related to the study drug.

- *Considerations: Contributing factors for the pulmonary embolism, cardiovascular history (hypertension, mitral valve prolapse, atrial fibrillation, bifasciular block), history of lung disorder, and hereditary spherocytosis, and the patient being overweight as well as AD contributing to immobility.*

Case 15 Dona-PC (Pulmonary embolism; donanemab)

An 81-year-old White female (APOE ε4 heterozygote) with body mass index of 28.8 kg/m^2, smoking history (approximately 50 years prior to event), and receiving concomitant raloxifene was started on donanemab treatment with last dose on SD 141 (Visit 7). On SD 168 (Visit 8), the patient's MRI showed new ARIA-E Grade 2 mild in 2 locations and 2 new ARIA-H microhemorrhages without associated symptoms; the study drug was withheld. On SD 197, MRI showed complete resolution of ARIA-E and stabilization of ARIA-H (no change in the 2 microhemorrhages). The study drug was planned to be restarted on Day 224. On SD 215, 74 days since the last dose of donanemab, the patient died due to pulmonary embolism. The autopsy

results showed large saddle pulmonary embolism as the cause of death and the event was assessed as not related to the study drug.

- *Considerations: Contributing factors for the pulmonary embolism event included advanced age, patient being overweight, and concomitant use of raloxifene, which has pulmonary embolism listed as an ADR; last dose of donanemab was more than 2 months (75 days) prior to the pulmonary embolism event.*

Case 16 Dona-PC (Respiratory arrest; donanemab)

A 73-year-old White male (APOE ε4 heterozygote) with history of dyslipidemia, diabetes mellitus, alcohol use, and receiving nonsteroidal anti-inflammatory medication (ibuprofen) was started on donanemab treatment with last dose on SD 281 (Visit 12). The patient had SAEs of obstruction gastric (SD 298; suspected due to metastatic urothelial cancer on CT), delirium (SD 309), acute kidney injury (SD 313), pancreatitis (SD 315), and duodenitis (SD 327). Esophagogastroduodenoscopy showed extrinsic compression from a tumor. On SD 331, the patient died due to respiratory arrest. Death certificate stated cause of death was pulseless electrical activity arrest, the antecedent cause was a possible seizure, and the underlying cause was likely an obstructive lesion causing pancreatitis, duodenitis, and esophagitis. The investigator assessed the event as not related to the study drug.

- *Considerations: This case of respiratory arrest is likely a complication of multifactorial illness, including pancreatitis, suspected cancer, gastric obstruction due to possible extrinsic tumor compression, duodenitis with severe duodenal inflammation, prerenal acute kidney injury, right lower lobe dependent airspace disease suspicious for pneumonia, and possible seizure; in addition, the patient had history of dyslipidemia, diabetes mellitus, alcohol use, and concomitant use of nonsteroidal anti-inflammatory medication (ibuprofen) as risk factors.*

9.1.1.7. Psychiatric Disorders

Case 17 Dona-PC (Completed suicide; donanemab)

A 62-year-old White male (APOE ε4 heterozygote) with medical history of paranoia/delusions, hypothyroidism, circadian rhythm sleep disorder, and receiving mirtazapine as concomitant medication for the circadian rhythm sleep disorder was started on donanemab treatment. The last dose was on SD 140 (Visit 7). The patient responded affirmatively to “non-specific active suicidal thoughts” item on C-SSRS at Visits 2 and 3, but not at Visits 4 to 7. The patient had “episodes of anxiety” of moderate severity since SD 158 through SD 167, and severe “delusions” starting SD 169 and ongoing. Olanzapine was started on SD 172 for delusions. On SD 175, the patient completed suicide and the event was assessed as not related to the study drug.

- *Considerations: Patient’s medical history of paranoia/delusions and responses on the C-SSRS of suicidal thoughts.*

Case 18 Dona-PC (Completed suicide; donanemab)

A 77-year-old White male (APOE ε4 homozygote) patient with ongoing depression since SD -429 for which he was receiving duloxetine treatment was started on donanemab treatment with last dose on SD 309 (Visit 13). On SD 314, the patient completed suicide and the cause of death was reported as self-inflicted gunshot wound to the head. The patient did not have any affirmative response to suicidal ideation or behavior in C-SSRS during the duration of the study. The investigator assessed the event as not related to the study drug.

- *Considerations: History of long-standing depression that was possibly untreated. There is limited information regarding the circumstances that led to the completed suicide (for example, worsening of depression).*

9.1.2. Dona-PC: Placebo-Treated Patients

9.1.2.1. Nervous System Disorders

Case 19 Dona-PC (Dementia Alzheimer's type; placebo)

A 79-year-old White male (APOE ε4 heterozygote) with history of dementia Alzheimer's type, cerebral atrophy, sports injury, work injury, and hypertension was randomly assigned to placebo with the last dose on SD 512. An SAE of dementia Alzheimer's type (severe) was reported on SD 518, and the patient died due to worsening of dementia Alzheimer's type on SD 520. Death was not considered related to the study drug.

- *Considerations: Worsening of Alzheimer's disease is not infrequent during the natural course of the disease.*

9.1.2.2. General Disorders and Administration Site Conditions

Case 20 Dona-PC (Death; placebo)

An 85-year-old White male (APOE ε4 heterozygote) with history of hyperlipidemia, hypertension, sleep apnea, vertigo, bilateral total knee replacement, and spinal reconstruction surgery was started on placebo with the last dose on SD 198. An SAE of severe lower limb fracture (prolonged hospitalization due to broken leg and surgery) was reported (SD 199) and was ongoing at the time of death on SD 265. The patient died due to unknown reason, and the event was considered unrelated to the study drug.

- *Considerations: There is insufficient evidence regarding official cause of death including autopsy report/death certificate in this case; patient had a recent prolonged hospitalization due to broken leg as a potential contributing factor to death.*

9.1.2.3. Cardiac Disorders

Case 21 Dona-PC (Cardiac arrest; placebo)

A 79-year-old White female (APOE ε4 heterozygote), with no relevant medical history, was randomly assigned to placebo with the last dose on SD 90. An SAE of severe cardiac arrest was reported on SD 98 with death on SD 99. The patient was found in a slumped over position by a family member. Emergency services were called, and chest compression was performed by the

family member until emergency services arrived, but the patient was not revived. The cause of death was confirmed as cardiac arrest and myocardial infarction by investigator. In the opinion of the investigator, the SAE of cardiac arrest was not related to the study drug.

- *Considerations: Cardiac arrest can be attributed to complications of myocardial infarction, which occurs at increased rate in the elderly population, independent of drug exposure.*

Case 22 Dona-PC (Myocardial infarction; placebo)

A 75-year-old White female (APOE ε4 heterozygote) with medical history of angina pectoris, subclavian steal syndrome, transient ischemic attack, coronary artery disease, essential hypertension, and hyperlipidemia was started on placebo with the last dose on SD 231. On SD 249, the patient experienced heart attack (myocardial infarction) and died on SD 254. The event was assessed as not related to the study drug.

- *Considerations: For the myocardial infarction event was caused due to patient's advanced age and history of coronary artery disease, hypertension, and hyperlipidemia should be considered.*

9.1.2.4. Infections and Infestations

Case 23 Dona-PC (Pneumonia aspiration; placebo)

A 79-year-old White male (APOE ε4 heterozygote) with medical history of cardiac murmur (systolic murmur), carotid bruit (left and right carotid bruit), dyslipidemia, hypertension, and peripheral arterial occlusive disease was started on placebo with the last dose on SD 346. Severe acute respiratory syndrome from COVID-19 resulted in hospitalization for SAEs of pneumonia (community-acquired pneumonia) and acute myocardial infarction (non-ST elevation myocardial infarction) on SD 491. The patient recovered from these events by SD 512. On SD 551, the patient was hospitalized with SAE of pneumonia aspiration, was treated in the intensive care unit, and died on SD 558. The death was not considered related to the study drug.

- *Considerations: Aspiration pneumonia is not uncommon in the population, which occurs at an increased frequency in the treated disease state of dementia along with COVID-19. Study drug (placebo) was last administered approximately 6 and a half months prior.*

Case 24 Dona-PC (Pneumonia; placebo)

An 82-year-old White male (APOE ε4 status unknown) with history of hypertension, gastroesophageal reflux disease, tachycardia, hyperlipidemia, and ex-smoker was randomly assigned to placebo with the last dose on SD 57. On SD 126, SAEs of atrial fibrillation (moderate) and pneumonia (moderate) were reported followed by SAEs of bacterial sepsis (moderate), staphylococcal bacteremia (moderate), and staphylococcal infection (moderate) on SD 129. The patient died due to pneumonia on SD 139, and death was assessed as not related to the study drug.

- *Considerations: Pneumonia is a common event in the general population and occurs at an increased frequency in older patients with AD. Other considerations include history of smoking, cardiovascular risk factors, and sepsis.*

Case 25 Dona-PC (Pneumonia; placebo)

An 86-year-old White female (APOE ε4 noncarrier) with history of hypertension and chronic kidney disease was randomly assigned to placebo with the first and last dose on SD 1. The patient was moving to a different state. On SD 131, four months and ten days after the last dose of the study drug, the patient presented with history of shortness of breath, lethargy, weakness, loss of appetite, cough, and generalized body pain for few days, and was hospitalized with SAE of community-acquired pneumonia along with acute hypoxic respiratory failure, pulmonary hypertension, and acute kidney insufficiency on chronic kidney disease (all nonserious). On SD 147, the patient died due to pneumonia and the event was assessed as not related to the study drug.

- *Consideration: Pneumonia is a common event in the elderly population, and description of community-acquired pneumonia during the pandemic may represent COVID. Single dose of the study drug (placebo) was last administered more than 4 months prior to the event.*

Case 26 Dona-PC (Sepsis; placebo)

An 83-year-old White male (APOE ε4 homozygote) with history of prostate cancer, radiation treatment, gastrointestinal reflux disease, and concomitant use of heparin was started on placebo with the last dose on SD 224. SAEs of obstructive pancreatitis (severe) and bile duct stone (severe) were reported (SD 231), and the patient recovered by SD 240. On SD 240, an SAE of pneumonia aspiration (severe) was reported followed by an SAE of upper gastrointestinal hemorrhage (moderate) on SD 244. The patient was reported recovered from both by SD 269. On SD 281, the patient was hospitalized due to SAEs of sepsis (severe) and pneumonia aspiration (severe), was treated with piperacillin, and died due to sepsis (SD 291). The primary cause of death as per death certificate was sepsis with aspiration pneumonia, dysphagia, and prostate cancer. The investigator's assessment for all events was not related to the study drug.

- *Considerations: Fatal sepsis is plausible in this patient with aspiration pneumonia and advanced age.*

9.1.2.5. Respiratory, Thoracic, and Mediastinal Disorders

Case 27 Dona-PC (Respiratory failure; placebo)

An 85-year-old White male (APOE ε4 heterozygote) with relevant medical history of type 2 diabetes and obesity was started on placebo with an SAE of COVID-19 pneumonia (severe) reported on SD 9 and SAE of respiratory failure (severe) on SD 17. Treatment included remdesivir, steroids, supplemental oxygen, and placement on mechanical ventilation. On SD 28, the patient died due to respiratory failure. In the opinion of the study investigator, the SAEs were not related to the study drug.

- *Considerations: Respiratory failure associated with severe COVID-19 is plausible as a severe in a patient with type 2 diabetes, obesity and older age.*

9.1.2.6. Psychiatric Disorders

Case 28 Dona-PC (Completed suicide, carbon monoxide poisoning; placebo)

A 79-year-old White male patient (APOE ε4 heterozygote) with medical history of depression had been on escitalopram treatment from SD -34 until the event of death. The patient was randomly assigned to placebo, with the last dose given on SD 253. On SD 277, the patient committed suicide by carbon monoxide poisoning. The patient did not have any affirmative response to suicidal ideation or behavior in C-SSRS during the duration of the study. The site was unaware of any clinical/social circumstances prior to suicide, and there were no recent changes to concomitant medications. The event was not considered related to the study drug.

- *Considerations: Completed suicide in a patient with AD with preexisting history of depression is plausible although there are insufficient details about the circumstances, such as social and clinical, leading up to the event.*

9.1.2.7. Injury, Poisoning, and Procedural Complications

Case 29 Dona-PC (Respiratory fume inhalation disorder; placebo)

An 84-year-old White female (APOE ε4 heterozygote) with no relevant medical history was started on placebo, with last dose on SD 162. The patient died due to smoke inhalation from a house fire SD 176. The event was not assessed as related.

- *Considerations: Respiratory fume inhalation disorder is more likely related to external factors (house fire secondary to a natural disaster).*

9.1.2.8. Vascular Disorders

Case 30 Dona-PC (Arteriosclerosis; placebo)

A 66-year-old White female (APOE ε4 homozygote) with relevant medical history of hypercholesteremia and type 1 diabetes was randomly assigned to placebo, with last dose given on SD 341. Fatal SAE of arteriosclerosis (severe) was reported (SD 351), with no prior symptoms and no autopsy. Investigator reported the event as related to the study drug.

- *Considerations: For the arteriosclerosis event, the patient's history of hypercholesterolemia and type 1 diabetes are risk factors.*

9.1.3. All Dona

In All Dona, there were 18 additional deaths (Table 9.3) beyond those in the placebo-controlled period for an overall frequency of 1.3%. Of these additional fatal events, most were again a single type of event in patients with multiple risk factors. Three of these were notable, and narratives for these are included in Section 9.1.3.1:

- 1 fatal ARIA-E
- 1 death due to thalamic hemorrhage, which the investigator assessed as possibly related to donanemab, and
- 1 additional death due to intracranial hemorrhage in a patient given a thrombolytic to treat stroke-like symptoms.

Table 9.3. Case Summaries for Additional Adverse Events Leading to Death Occurring in All Dona, Prespecified Analysis

Case Number	Fatal Event	Day of Death	Demographics	Relevant Information	Days since Last Dose to Death
Donanemab-treated patients, n = 18					
31	Amyloid-related imaging abnormalities–edema	730	77, White, male	HTN, hyperlipidemia, CAD, MI, prolactin secreting tumor, APOE ε4 heterozygote	59
32	Hemorrhage intracranial	706	72, White, male	APOE ε4 heterozygote	13
33	Thalamus hemorrhage	421	77, White, male	HTN, DM, hyperlipidemia, Parkinsonism, and stroke	51
Other Unrelated Deaths – narratives not provided					
NP	Dementia with Lewy bodies	484	70, White, female	Cervical dystonia, dysphagia, severe dysphagia 27 days prior to death	311
NP	Metabolic encephalopathy	440	79, White, male	COVID-19 with sepsis and anemia, dysphagia, acute encephalopathy, acute hypoxic respiratory failure, azotemia, rhabdomyolysis, hypernatremia, and elevated blood glucose level	130
NP	Death	204	80, White, male	Chronic lymphocytic leukemia, DM, hyperlipidemia, HTN, CAD, ischemic heart disease, obesity, COPD, and sleep apnea	31
NP	Cardiac arrest	424	75, White, female	HTN, hyperlipidemia, depression	180
NP	Cardiac failure congestive	438	77, White, male	Cardiomyopathy, chronic systolic heart failure, premature ventricular contractions, DM, and hyperlipidemia	20
NP	Pneumonia aspiration	418	78, White, female	Carotid artery disease, HTN, DM, hyperlipidemia, atherosclerosis, left carotid artery stent placement, right carotid endarterectomy, peripheral artery disease, intermittent diarrhea with severe hypokalemia, and cardiac arrhythmia (SD 408)	361
NP	Dehydration, malnutrition, electrolyte imbalance, arrhythmia	628	84, White, female	HTN	4
NP	Acute respiratory failure	39	75, White, female	Pulmonary fibrosis with COPD. Acute mental status changes and severe acute respiratory failure (SD 38)	7
NP	Respiratory failure	282	85, White, female	Paroxysmal atrial fibrillation, coronary artery stent placement, hyperlipidemia, HTN, atherosclerosis of the aorta, pHTN, CAD, congestive heart failure, coronary artery bypass grafts. Severe carotid artery disease with stent placement (SD 280)	24
NP	Gun shot wound	41	83, White, male	No relevant medical history	12

Case Number	Fatal Event	Day of Death	Demographics	Relevant Information	Days since Last Dose to Death
NP	Head injury	345	87, White, male	HTN, coronary artery bypass, atrial fibrillation. Hx of fall with head trauma (SD 345)	33
NP	Pelvic fracture, pneumonia bacterial	441	81, White, male	COPD, osteoporosis, and vitamin D deficiency. Hx of fall (SD 286) and COVID-19 (SD 287)	270
NP	Aortic dissection, cardiac arrest	660	86, White, male	MI, cardiac stent, HTN, abdominal aortic aneurysm without rupture, abdominal aortic aneurysm repair, aneurysm of iliac artery, iliac artery stent, aortic valve regurgitation, coronary arteriosclerosis, and hyperlipidemia.	3
NP	Pancreatic carcinoma metastatic	431	80, White, male	Prostate cancer, DM	59
NP	Renal failure	702	65, White, female	HTN, Hx of renal failure and UTI (SD 689) with dysuria, hallucinations, vomiting, and loss of appetite	45

Abbreviations: APOE ε4 = allele subtype 4 of the gene coding for apolipoprotein class E; CAD = coronary artery disease; COPD = chronic obstructive pulmonary disease; COVID-19 = coronavirus disease 2019; DM = diabetes mellitus; HTN = hypertension; Hx = history; MI = myocardial ischemia; n = number of patients; NP = not provided; SD = study day; pHTN = pulmonary hypertension; UTI = urinary tract infection.

9.1.3.1. Nervous System Disorders

Case 31 All Dona (Amyloid-related imaging abnormalities–edema; donanemab)

A 77-year-old White male (APOE ε4 heterozygote) with hypertension, hyperlipidemia, coronary artery disease, myocardial infarction, and prolactin-producing pituitary tumor, prostate cancer, and with acetylsalicylic acid and donepezil as concomitant medications started on placebo. Screening MRI showed 1 microhemorrhage. From SD 96 (Visit 5) to SD 512 (Visit 21), the MRI remained unchanged from screening. On SD 567 (Visit 22), the patient started donanemab treatment in the AACI-LTE period. On SD 594 (Visit 23) and SD 631 (Visit 25), the patient's MRI scan remained unchanged from screening. The last dose (24th dose; fifth infusion of donanemab in the AACI-LTE period) was on SD 671 (Visit 26). On Day 694, 23 days after the second dose of 1400 mg donanemab, the patient was hospitalized with difficulty in walking, heightened confusion, severe headache, nausea, dizziness, unstable gait, and visual impairment. Symptomatic ARIA-E was reported with MRI showing a right parietal-occipital T2-FLAIR hyperintensity. On SD 696, the MRI showed a moderate T2 hyperintense lesion in the right occipital lobe with vasogenic edema and mild mass effect. On SD 699, IV methylprednisolone (1000 mg/day) treatment was initiated, which continued for 5 days. On SD 704, methylprednisolone treatment was transitioned to prednisone, and on SD 716, the patient's condition progressively worsened. MRI (SD 723) showed a decreased abnormal T2/FLAIR signal in the right occipital lobe with a resolution of surrounding mass effect and sulcal effacement. The patient was discharged to a nursing home facility and died on SD 730 due to ARIA-E.

- *Consideration: The fatal ARIA-E was considered related to donanemab treatment.*

Case 32 All Dona (Hemorrhage intracranial; donanemab)

A 72-year-old White male (APOE ε4 heterozygote) with no vascular risk factors started on placebo in the AACI period on SD 1. Brain MRIs were normal up to SD 566. The patient started donanemab in AACI-LTE with last dose (fifth) of donanemab given on SD 693. On SD 702, the patient had an acute ischemic stroke, results of brain CT scan were normal, and the patient was treated with tenecteplase. Repeat CT scan on SD 702 showed multiple bilateral intracerebral hemorrhages, and the patient was given cryoprecipitate and fibrinogen. MRI (SD 702) after tenecteplase administration showed new severe ARIA-E, 4 new macrohemorrhages, 3 new areas of superficial siderosis, and intraventricular hemorrhage. The patient died on SD 706 due to bilateral intraparenchymal hemorrhage from tenecteplase and acute hypoxic respiratory failure. In the opinion of the investigator, intracranial hemorrhage was not related to the study drug, and hemorrhage could have been caused by the treatment with tenecteplase (reported as tissue plasminogen activator) and made worse by CAA and amyloid removal by the study drug.

- *Considerations: Intracranial hemorrhage can be attributed to the thrombolytic drug used for the treatment of ischemic stroke.*

Case 33 All Dona (Thalamus hemorrhage; donanemab)

A 77-year-old White male (APOE ε4 heterozygote) with hypertension, insulin-requiring type 2 diabetes mellitus, hyperlipidemia, Parkinsonism, and stroke fulfilled the dose-stopping criteria after receiving his 14th dose of donanemab on SD 370. The most recent brain MRI on SD 364 did not show any ARIA. On SD 409, the patient had a thalamic hemorrhage and died on SD 421. The cause of death was reported as thalamic hemorrhage. According to neurologist assessment, it was most likely hypertensive hemorrhage. Action with study drug was not applicable (the patient was not taking study drug at the time of the event). The event was considered as possibly related to donanemab treatment by the investigator.

- *Considerations: Contributing factors for the thalamus hemorrhage event included patient age and history of hypertension, hyperlipidemia, and stroke.*

9.2. Death Narratives for Within 76 weeks Approach (with Vital Status Update)

Based on the deaths occurring within 76 weeks of first dose, 3 of the deaths reported in the donanemab-treated group were related to donanemab treatment. Specifically, 2 were reported as ARIA (1 ARIA-E and 1 ARIA-H) and 1 event reported as "Death" occurred in a patient with ongoing serious ARIA-E and ARIA-H. The number of deaths for causes other than ARIA was similar across placebo and donanemab (n = 17 in the donanemab group and n = 17 in the placebo group).

Further review of the individual events in the donanemab-treated arm in the PC period by decreasing frequency showed

- 4 events in the General disorders and administration site conditions SOC compared to 7 events in placebo-treated patients:
  - 1 associated with ARIA that was discussed above
  - 1 patient who died in her sleep with a previous nonserious AE of peripheral edema, and
  - 2 patients were identified from the vital status search with death occurring 132 or 145 days after the last dose of donanemab and cause of death not provided. In the placebo group, 6 patients were identified with cause of death not provided.
- 4 events in the Infections and infestations SOC compared to 3 events in placebo-treated patients:
  - 2 events of pneumonia for the donanemab-treated arm compared to 2 events in placebo-treated patients. 1 donanemab-treated patient had pneumonia possibly due to aspiration. Another patient that discontinued due to hypersensitivity upon second infusion developed pneumonia and died 195 days after last dose of donanemab.
  - 1 event of COVID 19 and 1 event of COVID 19 pneumonia were reported in the donanemab treatment arm which is not unexpected during the pandemic in an AD population.
- 4 events in the Nervous system disorders SOC compared to 1 in placebo-treated patients:
  - 1 fatal ARIA H and 1 fatal ARIA H discussed above- both related to donanemab

    - 1 subarachnoid hemorrhage after a fall in a patient who was randomly assigned to donanemab and had received 2 infusions of saline after meeting amyloid clearance in Dona-PC, and
    - 1 event of Dementia Alzheimer's type after multiple SAEs of erosive gastritis and esophagitis compared to 1 placebo patient dying from this event.
- 4 events in donanemab-treated patients in Respiratory, thoracic and mediastinal disorders SOC compared to 1 placebo-treated patient:
    - 2 patients died from a pulmonary embolism where each had multiple risk factors
    - 1 patient died from respiratory arrest 50 days after the last dose of donanemab, likely as a complication of multi-factorial illness
    - 1 patient died from respiratory failure 184 days after the last dose of donanemab and after pneumonia. In the placebo-treated group, 1 patient also died from respiratory failure.
- 2 suicides in the donanemab group compared with 1 suicide in the placebo group, and
- all other deaths were from single type of event in patients with risk factors.

An evaluation of the fatal events beyond those related to ARIA were primarily explained by patient age, disease progression, comorbidities in patient medical history, the use of confounding concomitant medications and/or were long after (more than 5 half-lives) donanemab treatment. Most events presented with multiple risk factors. Beyond the 3 deaths associated with ARIA, the other events in the donanemab group had no discernible pattern or trend in the type of event, timing, frequency, or nature of the events that led to death, and all were assessed as not related to donanemab by the study investigator and sponsor.

Table 9.4. Case Summaries for Adverse Events Leading to Death Occurring in Dona-PC within 76 weeks Approach (with Vital Status Update)

Case Number	Fatal Event	Day of Death	Demographics	Relevant Information	Days since Last Dose to Death
Donanemab-treated patients, n = 20					
1	Amyloid-related imaging abnormalities– microhemorrhages and hemosiderin deposits	75	73, White, male	HTN, hypercholesterolemia, APOE ε4 noncarrier, baseline superficial siderosis (50 mm)	46
2	ARIA-E	80	73, White, female	MRI normal at screening, APOE ε4 heterozygote	24
4	Dementia Alzheimer's type	154	84, White, female	GERD, SAEs of erosive gastritis, esophagitis, hypertensive emergency, previous MI	56
5	Subarachnoid hemorrhage	244	84, White, male	Hx of HTN and fall. Fall on SD 237 with vertebral fracture.	82
6	Death	447	76, White, male	SAEs of ARIA on rechallenge, APOE ε4 heterozygote	48
7	Death	63	83, White, female	HTN, osteopenia, hyperlipidemia, basal cell carcinoma, and mild peripheral edema (SD 41); patient died during sleep.	34
9	COVID-19	352	80, White, male	AFIB, HTN, cardiomegaly, COPD	15
10	COVID-19 pneumonia	85	82, White, male	HTN, T2DM asthma, nephropathy	30
11	Pneumonia	36	85, White, female	Coronary artery bypass, TIA, nephropathy, HTN	5
12	Retroperitoneal hemorrhage	273	82, White, female	HTN, MI, pHTN, cardiac valve disease, and failure	18
13	Dehydration	81	68, White, male	HTN, T2DM, pneumonia, visual hallucinations	58
14	Pulmonary embolism	3	69, White, female	AFIB, mitral valve prolapse, HTN, lung disorder, T2DM, sleep apnea, hereditary spherocytosis	2
15	Pulmonary embolism	215	81, White, female	Smoker, concomitant raloxifene (PE in label)	74
16	Respiratory arrest	331	73, White, male	Dyslipidemia, DM, carotid artery disease and stenosis, alcohol use	50
17	Completed suicide	175	62, White, male	Paranoia/delusions hypothyroidism and circadian rhythm sleep disorder, sleep apnea	35
18	Completed suicide	314	77, White, male	Ongoing depression	5

Case Number	Fatal Event	Day of Death	Demographics	Relevant Information	Days since Last Dose to Death
34	Death (Vital status)	527	75, White male	Neuropathy peripheral, and glomerulonephritis.	132
35	Death (Vital status)	259	75, White, female	Cerebrovascular disorde, essential HTN, hypercalcaemia, and hypercolesterolaemia	145
36	Respiratory failure	514	77, White, female	HTN and hyperlipidemia.	184
37	Pneumonia	223	85, White, female	Bilateral carotid endarterectomy, urinary incontinence	195
Placebo-treated patients, n = 17					
19	Dementia Alzheimer's type	520	79, White, male	Dementia, cerebral atrophy, HTN, sports injury, and work injury	8
20	Death	265	85, White, male	History of bilateral knee replacement, spinal surgery, and prolonged hospitalization due to lower limb fracture	67
21	Cardiac arrest	99	79, White, female	Found unresponsive, was not revived	9
22	Myocardial infarction	254	75, White, female	Angina, HTN, TIA, CAD.	23
24	Pneumonia	139	82, White, male	History of smoking, HTN, tachycardia, with SAEs of AFIB, pneumonia, sepsis	82
25	Pneumonia	147	86, White, female	History of HTN, CKD-developed lethargy, weakness, hypoxia	146
26	Sepsis	291	83, White, male	History of prostate cancer and radiation with SAEs of obstructive pancreatitis, bile stones, aspiration pneumonia, GI bleeding and sepsis	67
27	Respiratory failure	28	85, White, male	T2DM, obesity with SAE of COVID-19	27
28	Completed suicide, carbon monoxide poisoning	277	79, White, male	History of depression with treatment, no affirmative response on C-SSRS	24
29	Respiratory fume inhalation disorder	176	84, White, female	Smoke inhalation secondary to house fire from natural disaster	14
30	Arteriosclerosis	351	66, White, female	Hypercholesteremia, T1DM, no prior symptoms	10
38	Death (Vital status)	442	76, White, female	Hypothyroidism, and uterine leiomyoma	186

Case Number	Fatal Event	Day of Death	Demographics	Relevant Information	Days since Last Dose to Death
39	Death (Vital status)	478	70, White, female	Hyperlipdemia, HTN, DM, NASH liver, cardiac catheterization, GERD, gastritis, gastric polypectomy and sinus bradycardia	141
40	Death (Vital status)	510	60, White, female	DM, rheumatoid arthritis and HTN	83
41	Death (Vital status)	448	80, White, male	Large intestine benign neoplasm, hyperlipidemia, essential HTN, COPD and diverticulum intestinal.	62
42	Death (Vital status)	404	77, Black, male	Emphysema, and COPD	95
43	Death (Vital status)	337	83, White, male	DM, diabetic neuropathy, HTN, and edema peripheral	139

Abbreviations: AFIB = atrial fibrillation; APOE ε4 = allele subtype 4 of the gene coding for apolipoprotein class E; ARIA = amyloid-related imaging abnormalities; CAD = coronary artery disease; CKD = chronic kidney disease; COPD = chronic obstructive pulmonary disease; COVID-19 = coronavirus disease 2019; C-SSRS = Columbia-Suicide Severity Rating Scale; DM = diabetes mellitus; GERD = gastroesophageal reflux disease; HTN = hypertension; Hx = history; MI = myocardial ischemia; MRI = magnetic resonance imaging; n = number of patients; NASH = non-alcoholic steatohepatitis; PC = placebo controlled; PE = pulmonary embolism; pHTN = pulmonary hypertension; SAE = serious adverse event; SD = study day; T1DM = type 1 diabetes; T2DM = type 2 diabetes mellitus; TIA = transient ischemic attack.

Case 34 (Vital status update; donanemab)

A 75-year-old White male (APOE ε4 heterozygote) with relevant medical history of dementia Alzheimer's type, neuropathy peripheral, and glomerulonephritis. The patient started to receive donanemab on SD 1 with last dose (15th dose) on SD 395. Last MRI, on SD 365, showed no findings suggestive of ARIA-E or ARIA-H. On SD 423, the patient discontinued treatment due to progressive disease. As of 08 May 2024, vital status was updated as patient passed away on SD 527.

Case 35 (Vital status update; donanemab)

A 75-year-old White female (APOE ε4 heterozygote) with relevant medical history of cerebrovascular disorder, dementia Alzheimer's type, essential hypertension, hypercalcaemia, and hypercolesterolaemia. The patient started to receive donanemab on SD 1 with last dose (5th dose) on SD 114. Last MRI, on SD 79, showed no findings suggestive of ARIA-E or ARIA-H. On SD 177, the patient discontinued treatment due to progressive disease. As of 08 May 2024, vital status was updated as patient passed away on SD 259.

Case 36 (Respiratory Failure; donanemab)

A 77-year-old White female (APOE ε4 heterozygote), with a relevant medical history of hypertension and hyperlipidemia. The patient started to receive donanenamb in the AACI-PC period on Study Day 1 (Visit 2). The last dose (13th dose) of the study drug prior to the SAEs was on Study Day 330 (Visit 14), which was final dose. Last MRI, on SD 176, showed no findings suggestive of ARIA-E or ARIA-H. On Study Day 356, an SAE of pneumonia (severe) was reported and on Study Day 366, the patient recovered from the event. On Study Day 386 (Visit 15), the patient permanently discontinued the study drug due to the event of pneumonia. On Study Day 514, six months and one day after the last dose of donanemab, the patient died due to respiratory failure. The patient's death certificate reported the immediate cause of death as cardiac arrest, primary cause of death as unspecified dementia, and secondary cause of death as chronic respiratory failure. No autopsy was performed.

Case 37 (Pneumonia; donanemab)

An 85-year-old White female (APOE ε4 heterozygote), with history of urinary incontinence and bilateral carotid endarterectomy. The patient started to receive donanemab in the AACI-PC period on Study Day 1 (Visit 2). On Study Day 28 (Visit 3), during the administration of 2nd dose of study drug, the patient experienced an AE of hypersensitivity and recovered on the same day. On Study Day 28, donanemab was permanently discontinued due to the AE of hypersensitivity and this was the last dose of study drug. Last MRI, on SD 87, showed no findings suggestive of ARIA-E or ARIA-H. On Study Day 196, 5 months and 18 days after the last dose of donanemab, the patient was hospitalised due to an SAE of pneumonia (severe). Patient was found to have moderate atrial fibrillation (non-serious) of unknown cause and was being treated for urinary tract infection. Patient received diltiazem and intravenous antibiotics and was discharged from the hospital on Study Day 209. The outcome of the SAE of pneumonia was ongoing. On Study Day 214, patient was admitted to the hospital again with an SAE of pneumonia. On Study Day 223, the patient died due to pneumonia. An autopsy was not performed.

Case 38 (Vital status update; placebo)

A 76-year-old White female (APOE ε4 heterozygote) with relevant medical history of dementia Alzheimer's type, hypothyroidism, and uterine leiomyoma. The patient started to receive placebo on SD 1 with last dose (10th dose) on SD 256. On SD 319, the patient discontinued treatment due to subject's decision. As of 08 May 2024, vital status was updated as patient passed away on SD 442.

Case 39 (Vital status update; placebo)

A 70-year-old White female (APOE ε4 heterozygote) with relevant medical history of hyperlipdaemia, hypertension, diabetes mellitus, NASH liver, cardiac catheterization, GERD, gastritis, gastric polypectomy and sinus bradycardia. The patient started to receive placebo on SD 1 with last dose (13th dose) on SD 337. On SD 413, the patient discontinued treatment due to progressive disease. As of 08 May 2024, vital status was updated as patient passed away on SD 478.

Case 40 (Vital status update; placebo)

A 60-year-old White female (APOE ε4 non-carrier) with relevant medical history of diabetes mellitus, rheumatoid arthritis, dementia Alzheimer's type and hypertension. The patient started to receive placebo on SD 1 with last dose (16th dose) on SD 427. On SD 456, the patient discontinued treatment due to progressive disease. As of 08 May 2024, vital status was updated as patient passed away on SD 510.

Case 41 (Vital status update; placebo)

A 80-year-old White male (APOE ε4 non-carrier) with relevant medical history of large intestine benign neoplasm, hyperlipidaemia, dementia Alzheimer's type, essential hypertension, COPD and diverticulum intestinal. The patient started to receive placebo on SD 1 with last dose (4th dose) on SD 106. On SD 386, the patient discontinued treatment due to lost to follow up. As of 08 May 2024, vital status was updated as patient passed away on SD 448.

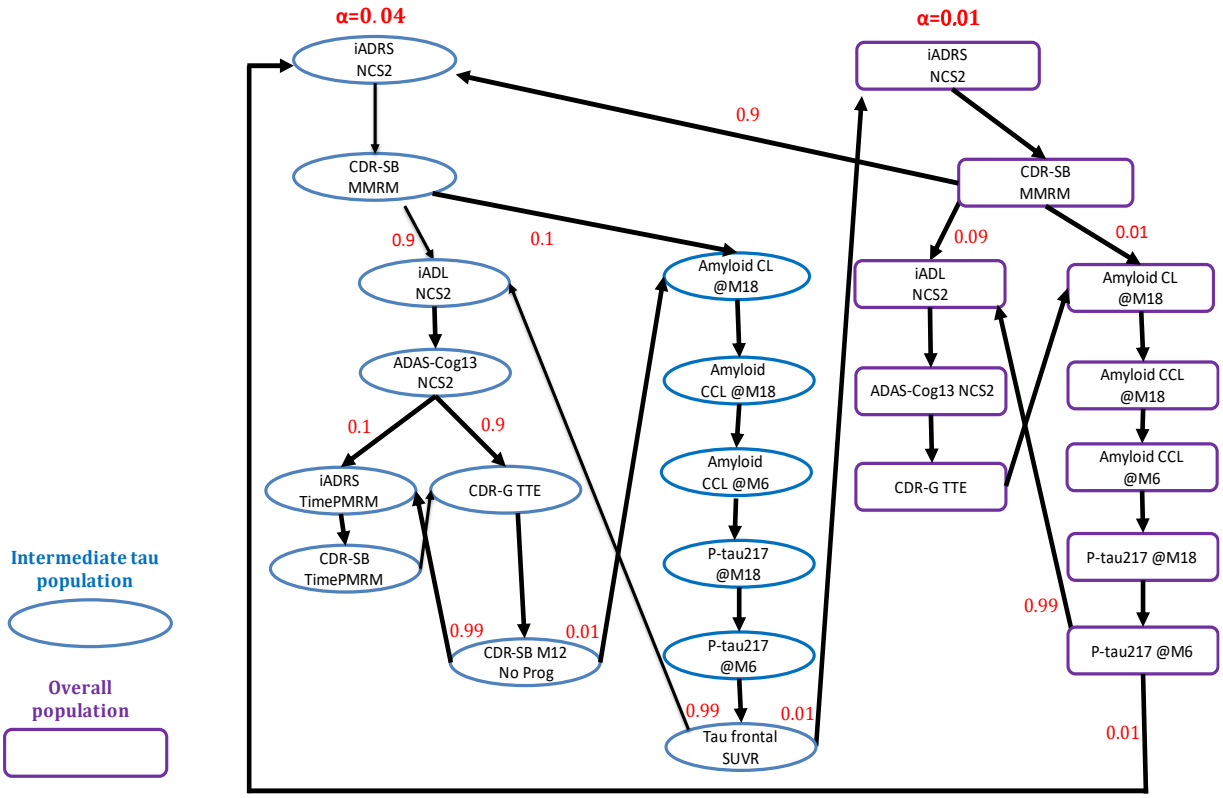
Case 42 (Vital status update; placebo)

A 77-year-old Black female (APOE ε4 non-carrier) with relevant medical history of dementia Alzheimer's type, emphysema, and COPD. The patient started to receive placebo on SD 1 with last dose (12th dose) on SD 309. On SD 326, the patient discontinued treatment due to caregiver circumstances. As of 08 May 2024, vital status was updated as patient passed away on SD 404.

Case 43 (Vital status update; placebo)

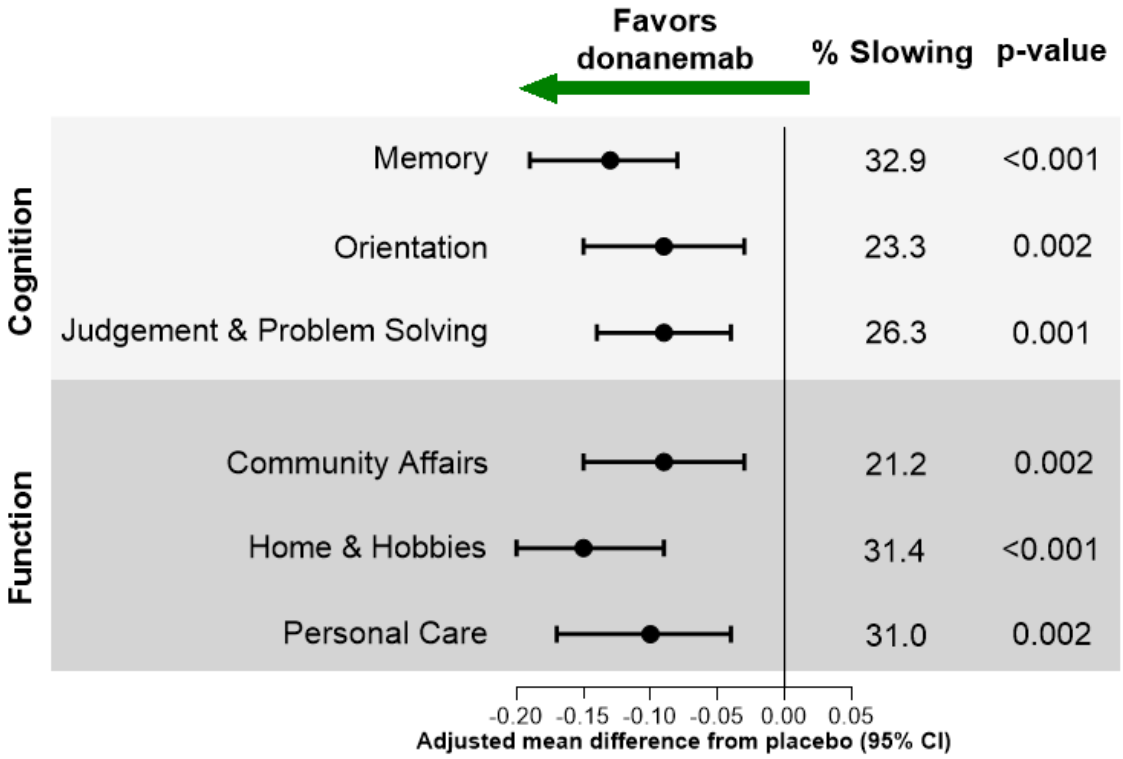
A 83-year-old White male (APOE ε4 non-carrier) with relevant medical history of dementia Alzheimer's type, diabetes mellitus, diabetic neuropathy, hypertension, and edema peripheral. The patient started to receive placebo on SD 1 with last dose (7th dose) on SD 198. On SD 282, the patient discontinued treatment due to caregiver circumstances. As of 08 May 2024, vital status was updated as patient passed away on SD 337.

9.3. Supporting Tables and Figures



Abbreviations: @M = at Month; ADAS-Cog$_{13}$ = Alzheimer's Disease Assessment Scale – 13-item Cognitive subscale; CDR-G = Clinical Dementia Rating Scale – Global score; CDR-SB = Clinical Dementia Rating Scale – Sum of Boxes; CL = Centiloid; iADRS = integrated Alzheimer's Disease Rating Scale; iADL = instrumental Activities of Daily Living subscale; PMRM = progression model for repeated measures; NCS2 = natural cubic spline model with 2 degrees of freedom; MMRM = Mixed Model for Repeated Measures; NCS = natural cubic spline; PC = placebo controlled; PET = positron emission tomography; P-tau217 = tau phosphorylated at threonine 217, also called phospho-tau 217; SUVR = standardized uptake value ratio; TTE = time to event.

Figure 9.1. Hypothesis testing scheme for controlling study-wise type I error rate at 2-sided 5%, Study AACI.



Abbreviations: CDR-SB = Clinical Dementia Rating Scale – Sum of Boxes; CI = confidence interval.

Figure 9.2. Clinically relevant treatment effect seen across all scale areas for CDR-SB at 76 weeks (Overall Population).

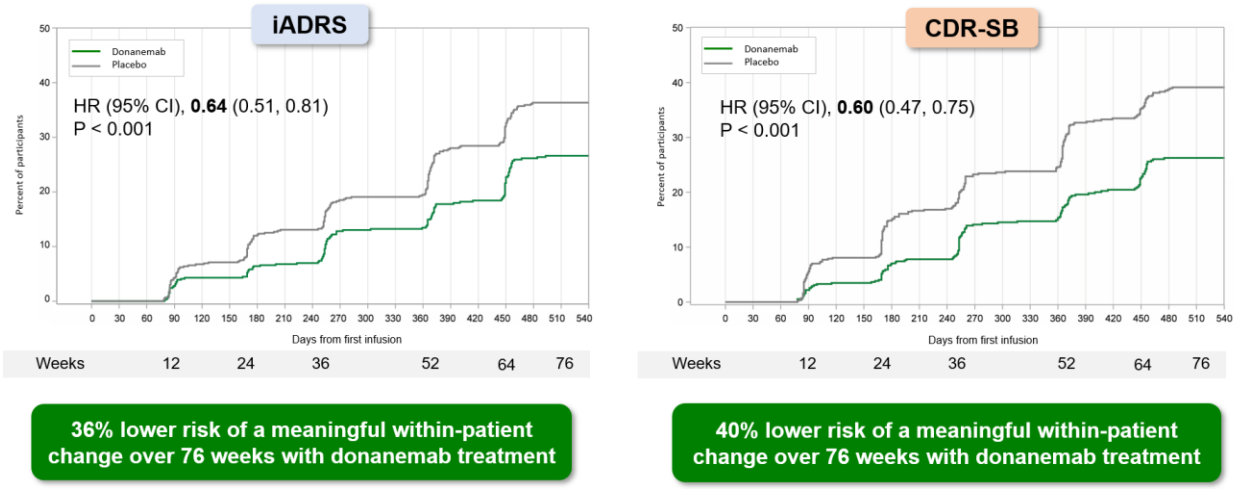
Table 9.5. Time-Saved Progression Model for Repeated Measures at Week 76, Low-Medium Tau Population, Study AACI

Time-PMRM	iADRS[a]	CDR-SB
Time saved[b] (95% CI)	4.36 (1.87, 6.85)	7.53 (5.69, 9.36)
p-Value	<0.001	<0.001
% time slowing	24.9	42.9

Abbreviations: AACI = I5T-MC-AACI; CDR-SB = Clinical Dementia Rating Scale – Sum of Boxes; CI = confidence interval; iADRS = integrated Alzheimer's Disease Rating Scale; PMRM = progression model for repeated measures.

[a] Results based on Time-PMRM nonproportionality model.

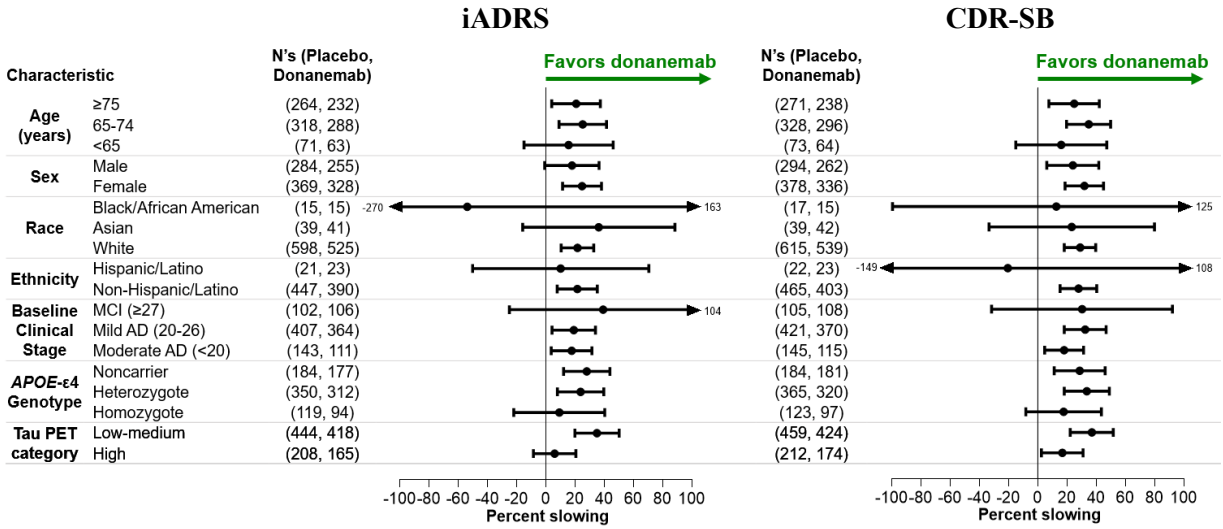
[b] Time saved in months.



Abbreviations: AD = Alzheimer's disease; CDR-SB = Clinical Dementia Rating Scale – Sum of Boxes; CI = confidence interval; HR = hazard ratio; iADRS = integrated Alzheimer's Disease Rating Scale; MCI = mild cognitive impairment.

Note: Meaningful within-patient change for iADRS was a change of ≥ -5 points for MCI due to AD and ≥ -9 points for mild AD dementia at 2 consecutive visits from baseline. Meaningful within-patient change for CDR-SB was a change of ≥1 point for MCI due to AD and ≥2 points for mild AD dementia at 2 consecutive visits from baseline.

Figure 9.3. Risk of meaningful within-patient change (low-medium tau population), Study AACI.



Abbreviations: AD = Alzheimer's disease; APOE = gene coding for apolipoprotein class E; CDR-SB = Clinical Dementia Rating Scale – Sum of Boxes; iADRS = integrated Alzheimer's Disease Rating Scale; MCI = mild cognitive impairment; N = number of patients; NCS = natural cubic spline; PET = positron emission tomography.

Note: NCS model with 2 degrees of freedom adjusted for basis expansion terms (2 terms), basis expansion term-by-treatment interaction, and covariates for age at baseline, pooled investigator, baseline tau level, and baseline acetylcholinesterase inhibitor/memantine use. Additional fixed terms include subgroup by treatment, subgroup by basis expansion, and subgroup by basis expansion by treatment interactions. Bars show the 95% confidence intervals; values are included for those that extend past the limits of the axis.

Figure 9.4. Subgroup analyses (Overall Population), Study AACI.

Table 9.6. Key Clinical Endpoints across Tau Groups, Study AACI

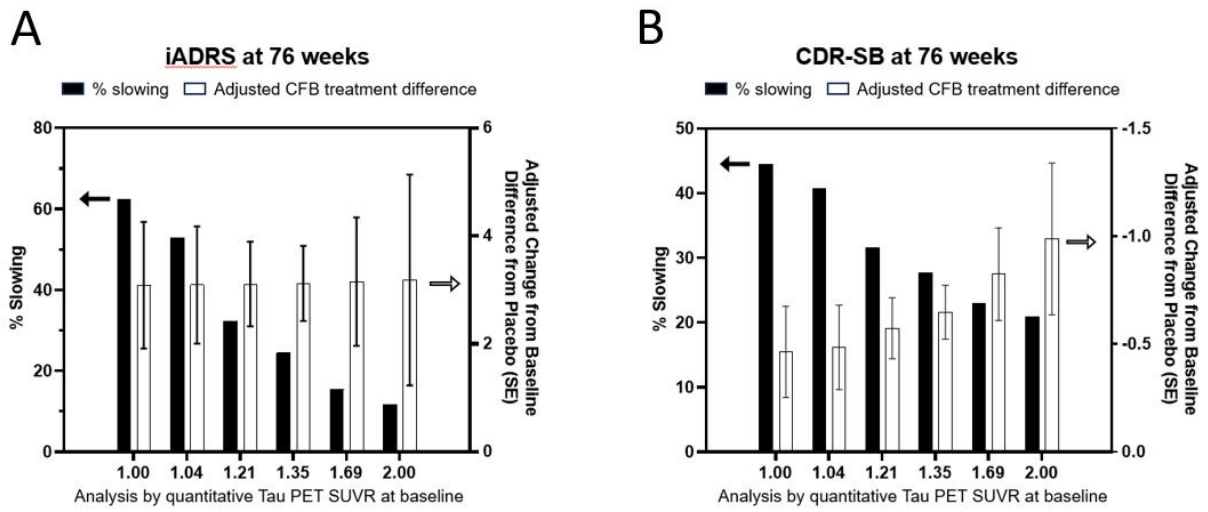
	Overall		Low-Medium Tau		High Tau[a]	
	Placebo N = 876	**Donanemab N = 860**	**Placebo N = 594**	**Donanemab N = 588**	**Placebo N = 281**	**Donanemab N = 271**
iADRS[b]						
Mean baseline	103.82	104.55	105.95	105.92	99.27	101.51
Change from baseline	-13.11	-10.19	-9.27	-6.02	-20.76	-19.51
Difference from placebo (%)	–	2.92 (22%) p<0.001	–	3.25 (35%) p<0.001	–	1.26 (6%) p = 0.415
CDR-SB[c]						
Mean baseline	3.89	3.92	3.64	3.72	4.43	4.36
Change from baseline	2.42	1.72	1.88	1.20	3.34	2.64
Difference from placebo (%)	–	-0.70 (29%) p<0.001	–	-0.67 (36%) p<0.001	–	-0.69 (21%) p = 0.006
ADAS-Cog$_{13}$[b]						
Mean baseline	29.16	28.53	27.60	27.41	32.42	31.02
Change from baseline	6.79	5.46	4.69	3.17	11.08	10.57
Difference from placebo (%)	–	-1.33 (20%) p<0.001	–	-1.52 (32%) p<0.001	–	-0.51 (5%) p = 0.531
ADCS-iADL[b]						
Mean baseline	47.98	47.96	48.56	48.20	46.71	47.42
Change from baseline	-6.13	-4.42	-4.59	-2.76	-9.25	-8.24
Difference from placebo (%)	–	1.70 (28%) p<0.001	–	1.83 (40%) p<0.001	–	1.01 (11%) p = 0.264

Abbreviations: ADAS-Cog$_{13}$ = Alzheimer's Disease Assessment Scale – 13-item Cognitive Subscale; ADCS-iADL = Alzheimer's Disease Cooperative Study – instrumental Activities of Daily Living subscale; CDR-SB = Clinical Dementia Rating – Sum of Boxes; iADRS = integrated Alzheimer's Disease Rating Scale; MMRM = mixed model for repeated measures; n = number of patients in the specified category; N = number of patients in the population; NCS2 = natural cubic spline with 2 degrees of freedom.

[a] High tau was a small subpopulation that was not statistically powered in Study AACI.

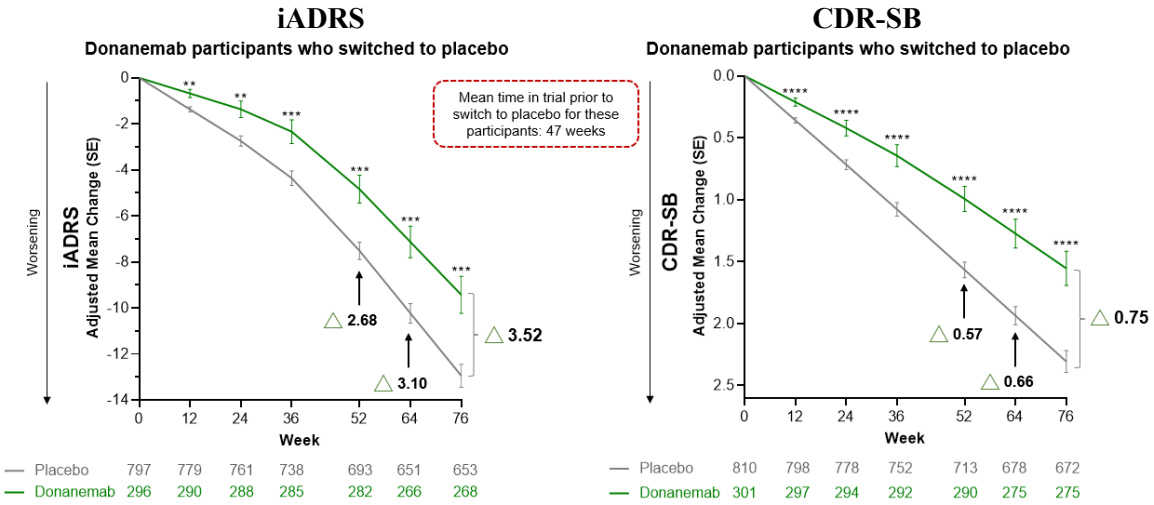
[b] NCS2 analysis.

[c] MMRM analysis.



Abbreviations: CDR-SB = Clinical Dementia Rating Scale – Sum of Boxes; CFB = change from baseline; iADRS = integrated Alzheimer's Disease Rating Scale; MMRM = mixed model for repeated measures; PET = positron emission tomography; SE = standard error; SUVr/SUVR = standardized uptake value ratio

Figure 9.5. MMRM analysis of iADRS (A) and CDR-SB (B) at 76 weeks according to quantitative SUVr, Study AACI.



Abbreviations: CDR-SB = Clinical Dementia Rating Scale – Sum of Boxes; iADRS = integrated Alzheimer's Disease Rating Scale; NCS = natural cubic spline; PET = positron emission tomography; SE = standard error.

Nominal P-values: ** p<0.01, *** p<0.001, **** p<0.0001.

Note: Average duration of treatment was 47 weeks.

iADRS and CDR-SB used the NCS model with 2 degrees of freedom adjusted for basis expansion terms (2 terms), basis expansion term-by-treatment interaction, and covariates for age at baseline, pooled investigator, baseline tau level, and baseline acetylcholinesterase inhibitor/memantine use. Patients that did not stop treatment were also included in the model but are not plotted here.

Figure 9.6. Treatment differences increase even after patients receive a reduction to placebo based on amyloid-imaging criteria on a 6- or 12-month PET scan (Overall Population), Study AACI.

Table 9.7. Demographics and Clinical Characteristics of Patients at Baseline, All Dona Population (AACG, AACI, AACN - Dona Cohort, AACI - Addendum, AACH)

Demographics	Donanemab (N = 2802)
Female sex, n (%)	1554 (55.5)
Mean age, years (SD)	74.2 (6.1)
Race, n (%)	
Asian	158 (5.7)
Black or African American	73 (2.6)
White	2552 (91.3)
Other[a]	12 (0.4)
Ethnicity Hispanic/Latino[b], n (%)	163 (7.3)
Education, ≥13 years, n (%)	1957 (71.7)
APOE ε4 carrier, n (%)	1890 (67.5)
APOE genotypes, n (%)	
E2/E2	1 (0.0)
E2/E3	69 (2.5)
E2/E4	84 (3.0)
E3/E3	832 (29.8)
E3/E4	1384 (49.6)
E4/E4	422 (15.1)
AChEI use, n (%)	1353 (48.3)
Memantine use at baseline, n (%)	553 (19.7)
AChEI and/or memantine use at baseline, n (%)	1518 (54.2)
Time since onset of AD symptoms (years), mean (SD)	4.1 (2.9)
Time since AD diagnosis (years), mean (SD)	1.5 (1.9)
Clinical category by MMSE at screening, n (%)	
Mild cognitive impairment (≥27)	613 (21.9)
Mild AD (20-26)	1859 (66.3)
Moderate AD (<20)	325 (11.6)
Amyloid plaque level in Centiloids (mean, SD)	95.5 (37.1)
Tau screening category (n,%)	
No tau	175 (8.7)
Very low	75 (3.7)
Low-medium	1271 (63.1)
High	494 (24.5)
missing	787

Abbreviations: AChEI = acetylcholinesterase inhibitor; AD = Alzheimer's disease; APOE ε4 = allele subtype 4 of the gene coding for apolipoprotein class E; MMSE = Mini-Mental State Examination; n = number of patients in the specified category; N = number of patients in the population; SD = standard deviation.

[a] Includes Multiple and American Indian or Alaskan Native.

[b] Only includes responses from the US or Puerto Rico sites for Study AACI.

Note: For all categories, the number of patients with nonmissing data was used as the denominator.

Table 9.8. Common (Occurred in at Least 5% of Patients) TEAEs by Preferred Term within System Organ Class, Donanemab Analysis Sets, End of Study Treatment Period Plus 57 Days

	AACI N = 1727		Dona-PC N = 1983		All Dona
Database lock date	**14 April 2023**		**07 June 2023**		**07 June 2023**
System Organ Class Preferred Term	**Placebo N = 874 n (%)**	**Donanemab N = 853 n (%)**	**Placebo N = 999 n (%)**	**Donanemab N = 984 n (%)**	**Donanemab N = 2802 n (%)**
Patients with 1 TEAE	718 (82.2)	759 (89.0)	831 (83.2)	879 (89.3)	2260 (80.7)
Nervous system disorders	298 (34.1)	456 (53.5)	354 (35.4)	527 (53.6)	1322 (47.2)
ARIA-E	17 (1.9)	205 (24.0)	18 (1.8)	240 (24.4)	570 (20.3)
ARIA-H	65 (7.4)	168 (19.7)	68 (6.8)	181 (18.4)	475 (17.0)
Superficial siderosis of central nervous system	10 (1.1)	58 (6.8)	14 (1.4)	76 (7.7)	158 (5.6)
Headache	86 (9.8)	119 (14.0)	102 (10.2)	129 (13.1)	311 (11.1)
Dizziness	48 (5.5)	53 (6.2)	63 (6.3)	64 (6.5)	155 (5.5)
Infections and infestations	350 (40.0)	277 (32.5)	391 (39.1)	324 (32.9)	922 (32.9)
COVID-19	154 (17.6)	136 (15.9)	162 (16.2)	140 (14.2)	427 (15.2)
Urinary tract infection	59 (6.8)	45 (5.3)	65 (6.5)	58 (5.9)	163 (5.8)
Injury, poisoning and procedural complications	207 (23.7)	260 (30.5)	242 (24.2)	298 (30.3)	784 (28.0)
Fall	110 (12.6)	114 (13.4)	129 (12.9)	132 (13.4)	340 (12.1)
Infusion-related reaction	4 (0.5)	74 (8.7)	4 (0.4)	84 (8.5)	234 (8.4)
Gastrointestinal disorders	169 (19.3)	178 (20.9)	194 (19.4)	212 (21.5)	456 (16.3)
Nausea	34 (3.9)	37 (4.3)	37 (3.7)	51 (5.2)	94 (3.4)
Musculoskeletal and connective tissue disorder	168 (19.2)	168 (19.7)	199 (19.9)	195 (19.8)	478 (17.1)
Arthralgia	42 (4.8)	49 (5.7)	53 (5.3)	60 (6.1)	114 (4.1)

Abbreviations: ARIA-E = amyloid-related imaging abnormalities–edema/effusions (also known as vasogenic edema); ARIA-H = amyloid-related imaging abnormalities–hemorrhage/hemosiderin deposition (including brain microhemorrhage and superficial siderosis); COVID-19 = coronavirus disease 2019; Dona = donanemab; LTE = long-term extension; MedDRA = Medical Dictionary for Regulatory Activities; n = number of patients with at least 1 TEAE; N = number of patients; PC = placebo controlled; TEAE = treatment-emergent adverse event.

Note: Patients are followed from the first dose of treatment to the end of treatment period +57 days, or the day prior to the first LTE visit, whichever occurs first.

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Table 9.9. Adverse Events Leading to Treatment Discontinuation by Preferred Terms within System Organ Class, Donanemab Analysis Sets, End of Study Treatment Period Plus 57 Days

	AACI N = 1727		Dona-PC N = 1983		All Dona
Database lock date	**14 April 2023**		**07 June 2023**		**07 June 2023**
System Organ Class Preferred Term	**Placebo N = 874 n (%)**	**Donanemab N = 853 n (%)**	**Placebo N = 999 n (%)**	**Donanemab N = 984 n (%)**	**Donanemab N = 2802 n (%)**
Discontinued Study Treatment due to an AE	38 (4.3)	112 (13.1)	46 (4.6)	153 (15.5)	295 (10.5)
Nervous system disorders	8 (0.9)	39 (4.6)	12 (1.2)	62 (6.3)	122 (4.4)
ARIA-E	3 (0.3)	21 (2.5)	4 (0.4)	28 (2.8)	54(1.9)
ARIA-H	2 (0.2)	7 (0.8)	2 (0.2)	10 (1.0)	24 (0.9)
Superficial siderosis of central nervous system	0	3 (0.4)	1 (0.1)	11 (1.1)	15 (0.5)
Injury, poisoning and procedural complications	2 (0.2)	32 (3.8)	2 (0.2)	39 (4.0)	86 (3.1)
Infusion-related reaction	0	31 (3.6)	0	38 (3.9)	81 (2.9)

Abbreviations: AE = adverse event; ARIA-E = amyloid-related imaging abnormalities–edema/effusions (also known as vasogenic edema); ARIA-H = amyloid-related imaging abnormalities–hemorrhage/hemosiderin deposition (including brain microhemorrhage and superficial siderosis); Dona = donanemab; LTE = long-term extension; MedDRA = Medical Dictionary for Regulatory Activities; n = number of patients with at least 1 TEAE; N = number of patients; PC = placebo controlled; TEAE = treatment-emergent adverse event.

Note: Patients are followed from the first dose of treatment to end of treatment period +57 days, or the day prior to the first LTE visit, whichever occurs first.

Table 9.10. Univariate Analysis with FDR Correction

Variable Name	Variable Description	p-Value	FDR-Adjusted p-Value
AGEGRP	Age group	<0.001	0.003
SSONLY	Presence superficial siderosis (Y/N)	0.006	0.055
DIABETES	History of diabetes	0.007	0.055
NASPATI	Non-aspirin antiplatelet usage	0.009	0.055
DISSTAT	Disease severity status (MCI, mild, moderate)	0.019	0.089
ASPATIP	Aspirin >81 mg daily or antiplatelet usage	0.071	0.284
CEREBROA	History of prior cerebrovascular accident	0.116	0.379
WMDSEV	Severity of white matter disease	0.126	0.379
HYPTENSN	History of hypertension	0.160	0.426
ANTICOG	Anticoagulant use	0.263	0.613
TRT01A[a]	Actual treatment for period 01	0.300	0.613
COVIDVBL	COVID vaccine	0.307	0.613
MICRONUM	Number of microhemorrhages	0.335	0.619
ADDUR	Duration of AD diagnosis (years)	0.361	0.619
CRBRODIS	History of cerebrovascular disorder	0.438	0.658
BFBPCLCT	Amyloid PET burden (tertiles category)	0.441	0.658
ASPNGT81	Aspirin >81 mg daily use	0.468	0.658
ASPRIN	Aspirin use	0.522	0.658
ETAUGRP	TAU group (medium, high)	0.542	0.658
COVIDIGH	History of COVID diagnosis	0.549	0.658
PNEUMNIA	History of pneumonia/infective pneumonia	0.606	0.679
MALTUMOR	History of prior cancer diagnosis w/in 5 years	0.623	0.679
APOEHOM	ApoE status	0.668	0.697
ANTITHFL	Antithrombotic use	0.870	0.870

Abbreviations: AD = Alzheimer's disease; APOE = gene coding for apolipoprotein class E; COVID = coronavirus FDR = false discovery rate; N = no; PET = positron emission tomography; Y = yes.

[a] TRT01A = variable for treatment with placebo vs donanemab.

Table 9.11. Sensitivity Analyses with Additional Analytical Approaches for Estimating Risk of Fatal Outcomes, Donanemab Placebo-Controlled Analysis Sets, End of Treatment Period Plus 57 Days

Analysis	AACI N = 1727 07 June 2023		Dona-PC N = 1983 07 June 2023	
	Placebo (N = 874)	Dona (N = 853)	Placebo (N = 999)	Dona (N = 984)
Death				
Hazard ratio (95% CI)[a]	--	1.78 (0.83, 4.03)	-	1.56 (0.76, 3.32)
p-value	--	0.143	--	0.230
Observation time-adjusted incidence rate per 100 patient-years[b] (95% CI)	0.8 (0.4, 1.5)	1.5 (0.8, 2.3)	0.8 (0.4, 1.5)	1.3 (0.8, 2.1)
Incidence rate difference (95% CI)	--	0.6 (-0.2, 1.5)	--	0.5 (-0.3, 1.3)
Incidence rate ratio[c] (95% CI)	--	1.79 (0.82, 3.92)	--	1.57 (0.76, 3.27)
p-value	--	0.142	--	0.224
Death (excluding 3 ARIA deaths)				
Hazard ratio[a]	--	1.47 (0.66, 3.40)	--	1.3 (0.61, 2.83)
p-value	--	0.353	--	0.500
Observation time-adjusted incidence rate per 100 patient-years[b] (95% CI)	0.8 (0.4, 1.5)	1.2 (0.7, 2.0)	0.8 (0.4, 1.5)	1.1 (0.6, 1.8)
Incidence rate difference (95% CI)	--	0.4 (-0.4, 1.2)	--	0.3 (-0.5, 1.0)
Incidence rate ratio[c] (95% CI)	--	1.48 (0.66, 3.33)	--	1.31 (0.61, 2.80)
p-value	--	0.346	--	0.486

Abbreviations: AACG = I5T-MC-AACG; AACI = I5T-MC-AACI; ARIA = amyloid-related imaging abnormalities; CI = confidence interval; Dona = donanemab; LTE = long-term extension; N = number of patients in the treatment group; PC = placebo controlled.

[a] Using Cox proportional hazards model.

[b] Incidence rate is 100 times the number of patients with an event divided by total time at risk, observed in years.

[c] Using Poisson regression model.

Note: Patients were included from the first dose of treatment to the end of treatment period +57 days, or the day prior to the first LTE visit, whichever occurs first.

Table 9.12. Sensitivity Analyses with Additional Analytical Approaches for Estimating Risk of Fatal Outcomes, Donanemab Placebo-Controlled Analysis Sets, with 76 Weeks Approach with Vital Status Update

Analysis	AACI N = 1727 07 June 2023		Dona-PC N = 1983 07 June 2023	
	Placebo (N = 874)	Dona (N = 853)	Placebo (N = 999)	Dona (N = 984)
Death				
Hazard ratio (95% CI)[a]	--	1.22 (0.63, 2.41)	--	1.20 (0.63, 2.33)
p-value	--	0.554	--	0.573
Observation time-adjusted incidence rate per 100 patient-years[b] (95% CI)	1.3 (0.8, 2.2)	1.6 (1.0, 2.5)	1.2 (0.7, 2.0)	1.5 (0.9, 2.3)
Incidence rate difference (95% CI)	--	0.3 (-0.7, 1.3)	--	0.2 (-0.6, 1.1)
Incidence rate ratio[c] (95% CI)	--	1.22 (0.63, 2.38)	--	1.21 (0.63, 2.30)
p-value	--	0.555	--	0.571
Death (excluding 3 ARIA deaths)				
Hazard ratio[a]	--	1.03 (0.51, 2.07)	--	1.02 (0.52, 2.02)
p-value	--	0.935	--	0.946
Observation time-adjusted incidence rate per 100 patient-years[b] (95% CI)	1.3 (0.8, 2.2)	1.4 (0.8, 2.2)	1.2 (0.7, 2.0)	1.3 (0.7, 2.0)
Incidence rate difference (95% CI)	--	0.04 (-0.9, 1.0)	--	0.02 (-0.8, 0.9)
Incidence rate ratio[c] (95% CI)	--	1.03 (0.51, 2.06)	--	1.02 (0.52, 2.01)
p-value	--	0.936	--	0.944

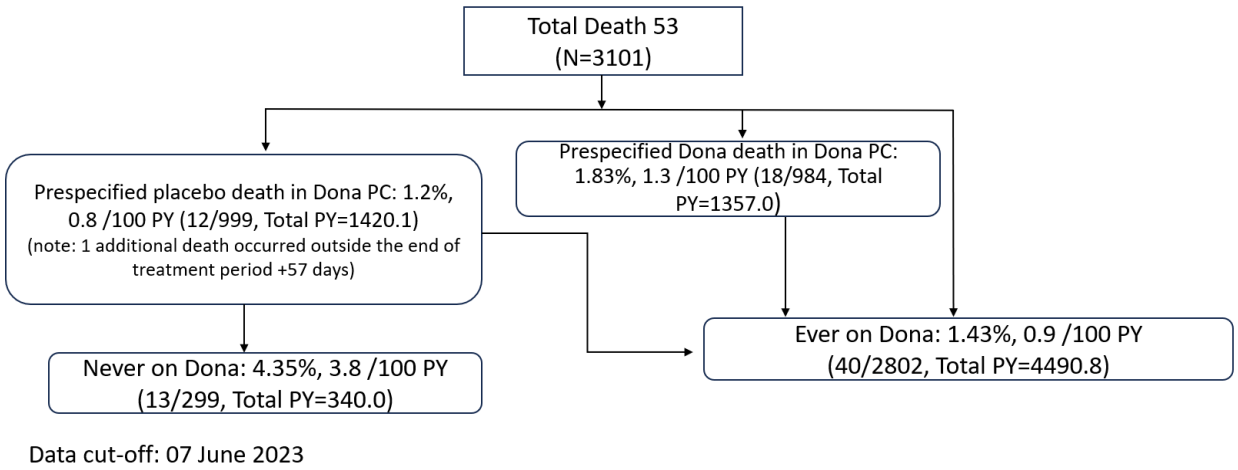
Abbreviations: AACG = I5T-MC-AACG; AACI = I5T-MC-AACI; ARIA = amyloid-related imaging abnormalities; CI = confidence interval; Dona = donanemab; LTE = long-term extension; N = number of patients in the treatment group; PC = placebo controlled.

[a] Using Cox proportional hazards model.

[b] Incidence rate is 100 times the number of patients with an event divided by total time at risk, observed in years.

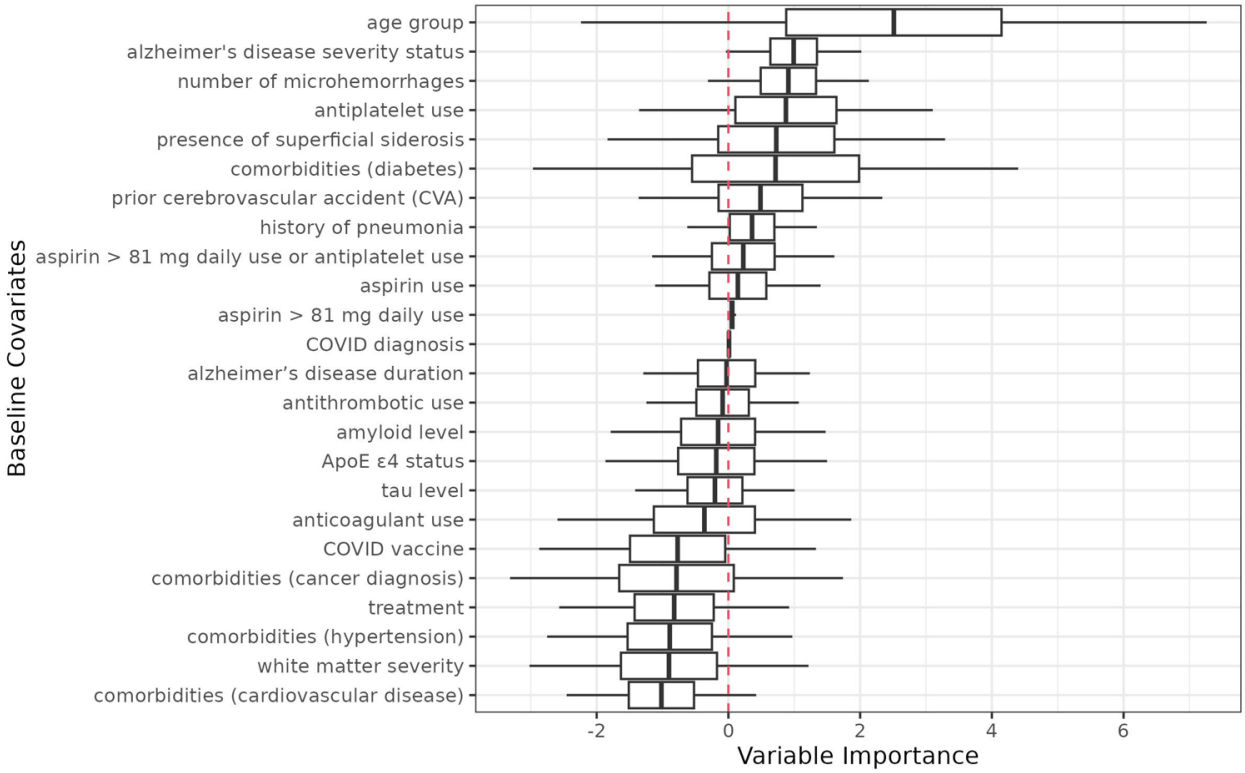
[c] Using Poisson regression model.

Note: Patients were included from the first dose of treatment to the end of treatment period +57 days, or the day prior to the first LTE visit, whichever occurs first.



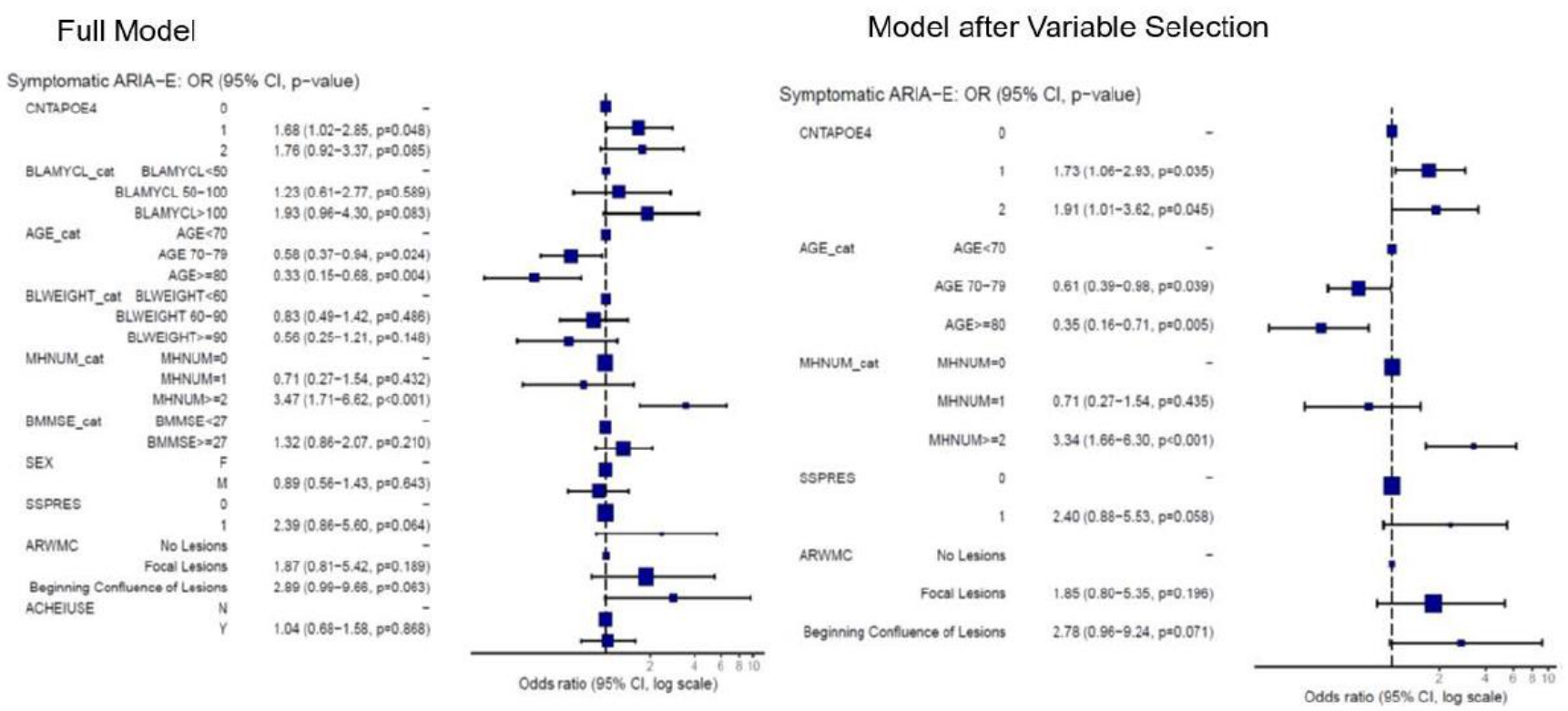
Abbreviations: Dona = donanemab; N = number of patients; PC = placebo controlled; PY = patient-years.

Figure 9.7. Total mortality in the integrated database.



Abbreviations: APOE = gene coding for apolipoprotein class E; COVID = coronavirus disease 2019.
Variable importance estimates of zero or less than zero indicate no evidence of a meaningful relationship between the input variable and risk of death. Variables for age and treatment assigned at baseline that are mentioned in the text are highlighted.

Figure 9.8. Variable importance (random survival forest).



Abbreviations: ACHIEUSE = acetylcholinesterase use; APOE = gene coding for apolipoprotein class E; ARIA-E = amyloid-related imaging abnormalities–edema/effusions; ARWMC = age-related white matter change; BLAMCYL = baseline amyloid in Centiloid categories; BLWEIGHT = baseline weight; BMMSE = baseline MMSE; CI = confidence interval; CNTAPOE = number of APOE ε4 alleles; Dona = donanemab; F = female; M = male; MHNUM = number of microhemorrhages; MMSE = Mini-Mental State Examination; MRI = magnetic resonance imaging; OR = odds ratio; SSPRES = superficial siderosis present; TE = treatment emergent; TEAE = treatment-emergent adverse event.

Figure 9.9. Forest plot of symptomatic ARIA-E (MRI or TEAE cluster) risk factor analysis, All Dona.