Received: 2 January 2025 | Revised: 13 February 2025 | Accepted: 13 February 2025

DOI: 10.1002/alz.70062

Alzheimer's & Dementia®
THE JOURNAL OF THE ALZHEIMER'S ASSOCIATION

RESEARCH ARTICLE

Modified titration of donanemab reduces ARIA risk and maintains amyloid reduction

Hong Wang[1] | Emel Serap Monkul Nery[1] | Paul Ardayfio[1] | Rashna Khanna[1] | Diana Otero Svaldi[1] | Ivelina Gueorguieva[1] | Sergey Shcherbinin[1] | Scott W. Andersen[1] | Paula M. Hauck[1] | Staci E. Engle[1] | Dawn A. Brooks[1] | Emily C. Collins[1] | Nick C. Fox[2] | Steven M. Greenberg[3] | Stephen Salloway[4,5] | Mark A. Mintun[1] | John R. Sims[1]

[1]Eli Lilly and Company, Indianapolis, Indiana, USA

[2]Dementia Research Centre, Department of Neurodegenerative Disease, and the UK Dementia Research Institute, UCL Queen Square Institute of Neurology, London, UK

[3]Department of Neurology, Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts, USA

[4]Butler Hospital, Providence, Rhode Island, USA

[5]Department of Neurology and Department of Psychiatry, Alpert Medical School of Brown University, Providence, Rhode Island, USA

Correspondence
John R. Sims, Eli Lilly and Company, Lilly Corporate Center, Indianapolis, IN 46285, USA.
Email: sims_john_r@lilly.com

Funding information
Eli Lilly and Company

Abstract

INTRODUCTION: TRAILBLAZER-ALZ 6 (NCT05738486) is a multicenter, double-blind, ongoing phase 3b study in early symptomatic Alzheimer's disease.

METHODS: Participants (n = 843) were randomized 1:1:1:1 (standard + three alternative donanemab dosing arms). Primary outcome was relative risk reduction (RRR) of amyloid-related imaging abnormalities with edema/effusions (ARIA-E) at 24 weeks assessed with Bayesian logistic regression. Amyloid plaque levels by positron emission tomography and serum donanemab pharmacokinetics were measured.

RESULTS: ARIA-E frequencies for standard, modified titration, dose skipping, and C_{max} arms were 23.7%, 13.7%, 18.6%, and 18.3%, respectively, at 24 weeks and similar at 52 weeks: 24.2%, 15.6%, 18.6%, and 18.8%, respectively. Modified titration met the 24-week primary outcome with 94% probability of achieving ≥ 20% RRR versus the standard arm. Modified titration also had significantly lower ARIA-E severity, but similar cumulative exposure and mean amyloid reduction compared to the standard arm.

DISCUSSION: Gradual up-titration of dose significantly reduced ARIA-E risk while demonstrating comparable pharmacokinetics/pharmacodynamics compared to standard dosing.

KEYWORDS
Alzheimer's disease, amyloid, amyloid-related imaging abnormalities, donanemab, phosphorylated tau217, titration

Highlights

- In TRAILBLAZER-ALZ 6, the amyloid-related imaging abnormalities-edema/effusions (ARIA-E) frequency was 13.7% in the modified titration arm compared to 23.7% in the standard arm at week 24.
- The modified titration arm met the primary endpoint of ARIA-E relative risk reduction at 24 weeks versus the standard arm.

Hong Wang and Emel Serap Monkul Nery contributed equally to this work.

- The modified titration versus standard arm at week 24 had comparable non-ARIA-E related safety profile, amyloid reduction, plasma phosphorylated tau217 reduction, cumulative exposure, and pharmacokinetics.
- Data at week 52 were consistent with week 24 results.

1 | BACKGROUND

Alzheimer's disease (AD) is an age-related neurodegenerative disorder characterized by progressive decline in cognitive and functional abilities. The number of people with mild cognitive impairment due to AD and AD dementia has been estimated to be 100 million globally.[1] Amyloid-targeting therapies, such as donanemab and lecanemab, are a class of drugs approved to treat AD.[2,3] While brain amyloid removal leads to significant slowing of AD progression, amyloid-related imaging abnormalities (ARIAs) are a well-recognized adverse event in clinical trials.[4–6] In TRAILBLAZER-ALZ 2, the 76-week, phase 3 donanemab trial, ARIAs with edema/effusions (ARIA-E) occurred in 24.0% and ARIAs with hemorrhages/hemosiderin deposition (ARIA-H) in 31.4% of donanemab-treated participants.[5]

Several baseline factors impact the risk of ARIA occurrence in participants treated with amyloid-targeting therapies. Participants who are apolipoprotein E (*APOE*) ε4 carriers have a greater risk of ARIAs than non-carriers, with homozygous carriers having the highest risk.[5–7] There is also increased risk when baseline magnetic resonance imaging (MRI) shows greater numbers of microhemorrhages and the presence of cortical superficial siderosis, recognized markers of cerebral amyloid angiopathy.[8–11]

Based on historical data, ARIA-E occurrence is more likely earlier in treatment, with nearly 90% of instances occurring within 6 months after treatment initiation.[2,4,5] Therefore, the timing and dosage of initial infusions are important considerations in ARIA-E reduction. The standard donanemab dosing regimen, which was implemented in TRAILBLAZER-ALZ 2, includes a titration period in which the first three doses are given once monthly at 700 mg before increasing to 1400 mg, which is then continued.[5] Here, we report the 24- and 52-week results of an ongoing phase 3b study investigating the effects of different donanemab dosing regimens on the frequency and severity of ARIAs and the extent of amyloid lowering in participants with early symptomatic AD.

2 | METHODS

2.1 | Study design

TRAILBLAZER-ALZ 6 (NCT05738486) is a multicenter, randomized, double-blind, phase 3b study in adults with early symptomatic AD and the presence of amyloid pathology assessed by positron emission tomography (PET) scans comparing the standard donanemab dosing regimen[2] to three alternative dosing arms. The first patient visit was in February 2023. The double-blind period of the study is 76 weeks. Participants ($N = 843$) were randomly assigned to the standard arm or one of three alternative arms in a 1:1:1:1 ratio. Participants were stratified by baseline amyloid PET scan results in Centiloids (CL; $24.1 \leq CL < 54$, $54 \leq CL < 79$, $79 \leq CL < 107$, or $CL \geq 107$) and *APOE* ε4 genotype (heterozygous carrier, homozygous carrier, or non-carrier). The four treatment arms varied in donanemab dosage per infusion and frequency of dosing but the total donanemab exposure by week 16 was the same (Figure 1). Amyloid PET scans were scheduled at screening and weeks 24, 52, and 76. Participants met amyloid plaque reduction criteria for stopping treatment if amyloid levels decreased to < 11 CL at any one measure or 11 CL to < 25 CL at two consecutive measures. MRI of the brain was scheduled at screening and weeks 4, 12, 24, and 52 (matching the previous TRAILBLAZER-ALZ 2 study up to 52 weeks[5]) to monitor for ARIAs and other clinically relevant safety findings. Additional unscheduled MRIs were recommended if participants presented with ARIA symptoms, or for monitoring purposes if ARIAs were detected, following the criteria used in TRAILBLAZER-ALZ 2.[5]

The protocol was approved by local ethical review boards and was conducted in accordance with the protocol and consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines, applicable International Conference on Harmonization Guideline for Good Clinical Practice, and all applicable laws and regulations.

2.2 | Participants

Participants were eligible for inclusion in the study if they were aged 60 to 85 years with gradual and progressive change in memory function for 6 or more months; Mini-Mental State Examination score of 20 to 28 (inclusive) at visit 1; and an amyloid PET scan result from a central read, consistent with the presence of amyloid pathology.

Participants were excluded from the study if they had a significant neurological disease affecting the central nervous system (other than AD) that could affect cognition or their ability to complete the study, including but not limited to, other dementias, serious infection of the brain, Parkinson's disease, multiple concussions, or epilepsy or recurrent seizures, except febrile childhood seizures; any contraindications for MRI or PET; and a centrally read screening MRI demonstrating the presence of ARIA-E, more than four cerebral microhemorrhages, more than one area of cortical superficial siderosis, any macrohemorrhage (cerebral hemorrhage > 1 cm), or severe white matter disease

(Fazekas score 3[12]). The fact that TRAILBLAZER-ALZ 6 did not require participants to have confirmed tau pathology is a key difference from the TRAILBLAZER-ALZ 2 randomized population, but it is consistent with the open-label exposure addendum of the TRAILBLAZER-ALZ 2 study.[5]

All patients gave informed consent for participation in the study prior to any study-specific procedures.

2.3 | Outcomes

The primary outcome was to assess the effect of alternative donanemab dosing regimens versus the standard donanemab dosing regimen (three once-monthly 700 mg doses followed by once-monthly 1400 mg) on ARIA-E frequency at 24 weeks. ARIA-E was the focus of the primary outcome given that most serious and symptomatic cases of ARIAs occur in the presence of ARIA-E, and ARIA-E is associated with treatment and not often spontaneous.

Secondary outcomes included the effects on brain amyloid deposition, the proportion of participants with any occurrence of ARIA-H, the severity of ARIA-E and ARIA-H, and donanemab serum pharmacokinetics. Tertiary and exploratory outcomes included blood-based biomarkers and the frequency and severity of infusion-related reaction events.

RESEARCH IN CONTEXT

1. **Systematic review**: Authors reviewed the literature (PubMed, meeting abstracts, and presentations) regarding amyloid-related imaging abnormalities (ARIAs) in Alzheimer's disease (AD) biology. ARIAs are not yet as widely studied as other aspects of AD; however, several recent publications have described clinical aspects. Relevant publications are appropriately cited.
2. **Interpretation**: The study investigated whether different donanemab dosing regimens, including standard, modified titration, dose skipping, and C_{max}, could reduce the frequency and severity of ARIAs with edema/effusions (ARIA-E) while maintaining donanemab's pharmacological effect (amyloid removal). The modified titration arm met the primary endpoint of ARIA-E reduction while maintaining amyloid removal.
3. **Future directions**: Understanding how dosing regimens for amyloid-targeting therapies may influence amyloid removal and ARIA frequency is critically important for future optimization of benefit and reduction of risk when treating early symptomatic AD.

2.4 | Pharmacokinetics

Pharmacokinetic analyses were conducted for participants who received at least one dose of investigational product and had blood samples collected. Samples for determination of donanemab serum concentration were collected as follows: pre-dose (before beginning the infusion) samples were collected from the intravenous site at weeks 4, 8, 12, and 24. Post-dose (within 30 minutes of completion of the infusion) samples for donanemab were collected at weeks 0, 4, 12, and 24. If donanemab infusion was permanently discontinued but the participant remained in the study, one pharmacokinetic sample was collected at the earliest scheduled visit. Population pharmacokinetic analyses were conducted.

2.5 | Pharmacodynamic effect and biomarkers

Acquisition, processing, and analysis of amyloid PET scans were conducted as previously described.[4,5] For the 24-week analysis, the effect on brain amyloid deposition of each alternative donanemab dosing regimen compared to the standard donanemab dosing regimen was assessed using an analysis of covariance (ANCOVA) model to derive least squares mean change in brain amyloid plaque from baseline. The ANCOVA model adjusted for baseline amyloid PET value as well as baseline age. For the analyses through 52 weeks, the effect of each alternative donanemab dosing regimen versus the standard donanemab dosing regimen on brain amyloid deposition was assessed using the mixed model for repeated measures (MMRM) methodology with fixed factors being treatment, visit, treatment-by-visit interaction, and covariates being baseline PET value, baseline PET value-by-visit interaction, and baseline age with an unstructured variance–covariance.

Plasma samples were collected at baseline and weeks 4, 8, 12, 24, 36, 52, 64, and 76. Plasma phosphorylated tau (p-tau)217 was assessed as an exploratory and supportive measure conducted on Eli Lilly and Company's Meso Scale Discovery platform and analyzed using the MMRM.[13]

2.6 | Statistical analyses

The primary endpoint was met if the posterior probability of an alternative dosing arm achieving at least 20% relative risk reduction (RRR) compared to the standard arm was > 80% by 24 weeks. The study was powered assuming a relative benefit of 40% reduction in ARIA-E risk by week 24 in each of the alternative arms compared to the standard arm. The ARIA-E rate by week 24 was assumed as 18.5% in the standard arm, based on observations from TRAILBLAZER-ALZ 2 open-label addendum data, and the false positive rate was controlled at a one-sided 5% level (if any of the three arms showed a risk reduction of at least 20% under the null, it was considered a false positive finding). The probability of study success and the false positive rate of the study under different assumptions of ARIA-E rates were determined by simulations using R version 4.1.2. Specifically, posterior samples

1:1:1:1 Randomization stratified by APOE and by baseline amyloid — Primary Outcome

Visit number	1	2	3	4	5	6	7	8	9	10	11	12
Study week	Screening	0	2	4	6	8	10	12	14	16	20	24
Standard		700	PBO	700	PBO	700	PBO	1400	PBO	1400	1400	1400
Modified titration		350	PBO	700	PBO	1050	PBO	1400	PBO	1400	1400	1400
Dose skipping		700	PBO	PBO	PBO	1400	PBO	1400	PBO	1400	1400	1400
Cmax		350	350	350	350	350	350	700	700	1400	1400	1400
Amyloid PET scan	√											√
MRI	√			√				√				√

350 = 1 x 350 mg vial
700 = 2 x 350 mg vials
1050 = 3 x 350 mg vials
1400 = 4 x 350 mg vials

FIGURE 1 Study design. All participants received a dosing regimen that included donanemab, but at different dose levels and frequency. Placebo was given at the indicated visits to preserve the blind for the different dosing schedules. The double-blind period of the study was 76 weeks. Total donanemab amounts were scheduled to be the same for the four dosing regimens. After week 16, participants in all arms were scheduled to receive 1400 mg of donanemab once monthly until dose-stopping criteria were met or the end of the study. An additional MRI occurred at week 52 and additional amyloid PET scans occurred at weeks 52 and 76. *APOE*, apolipoprotein E; C_{max}, maximum serum concentration; MRI, magnetic resonance imaging; PBO, placebo; PET, positron emission tomography

were generated through rjags package in R. The primary analysis used a Bayesian logistic regression model (including fixed effects for treatment regimen, *APOE* ε4 status, baseline presence of microhemorrhage, baseline presence of cortical superficial siderosis, and baseline amyloid level) to compare the relative reduction in ARIA-E frequencies by week 24 for the alternative arms versus the standard arm based on RRR estimates.

Cox proportional hazard models without factors beyond treatment groups were used for time-to-first-ARIA analyses.

All analyses related to safety, including analyses for the primary endpoint, were based on the safety analysis set defined as all participants randomly assigned to study treatment and who took at least one dose of study treatment.

3 | RESULTS

3.1 | Participants

A total of 2529 adults with early symptomatic AD were assessed for eligibility and 843 were randomized into the standard ($N = 208$), modified titration ($N = 212$), dose skipping ($N = 210$), and C_{max} ($N = 213$) arms (Figure S1A). Treatment disposition is shown in Figure S1B. The demographic and baseline characteristics were balanced across groups, including *APOE* ε4 carrier status, which was a stratification factor (Table 1).

The analyses presented in this report focus on the results of the 24-week donanemab treatment period and were based on a database lock date of August 2, 2024. Results of the 52-week donanemab treatment period based on a database lock date of October 19, 2024 are included to demonstrate data consistency. At the time of this report, the study is ongoing with the estimated last participant visit projected for mid-2025.

3.2 | ARIA-E

The primary outcome was ARIA-E frequency and RRR at 24 weeks. The percentage of participants who experienced ARIA-E was 23.7% for the standard arm, and 13.7%, 18.6%, and 18.3% for the three alternative dosing arms (modified titration, dose skipping, and C_{max}, respectively; Table 2 and Table S1). The modified titration arm met the primary objective (> 80% probability of achieving at least 20% RRR) with a posterior risk reduction (standard deviation [SD]) of 0.405 (0.123) and a 94.1% probability that the RRR was ≥ 20% (Table 2 and Table S2). The other alternative dosing regimens did not meet the prespecified success criteria (Table S2).

At 52 weeks, the percentage of participants who experienced ARIA-E was 24.2% for the standard arm, and 15.6%, 18.6%, and 18.8% for the three alternative dosing arms (modified titration, dose skipping, and C_{max}, respectively; Table S3 in supporting information). At 52 weeks the RRR of the modified titration arm was still significant (87% probability of achieving ≥ 20% RRR versus the standard arm; Table S4 in supporting information).

Due to significant differences only occurring between the standard and modified titration arms and the primary endpoint occurring at 24 weeks, the rest of this report will focus on the modified titration arm compared to the standard arm at 24 weeks. Corresponding data for all arms at 24 weeks and 52 weeks can be found in the supporting information.

The modified titration arm also met the secondary outcome measure of improved ARIA-E severity at 24 weeks. Radiographic severity of ARIA-E was significantly reduced compared to the standard arm ($P = 0.011$, Cochran–Mantel–Haenszel test). Notably, 86.3% of participants in the modified titration arm had no ARIA-E by MRI through week 24 (compared to 76.3% in the standard arm) and no radiographically severe events were observed (Figure 2A and Figure S2A; 52-week data: Figure S2B).

TABLE 1 Demographics and baseline characteristics of the population.[a]

Characteristics[a]	Standard (*N* = 208)	Modified titration (*N* = 212)	Dose skipping (*N* = 210)	C_{max} (*N* = 213)
Sex, female, *n* (%)	121 (58.2)	126 (59.4)	117 (55.7)	123 (57.7)
Age, mean (SD), in years	73.3 (5.7)	74.3 (5.7)	73.4 (5.8)	73.2 (6.0)
Race, *n* (%)				
Asian	0 (0)	3 (1.4)	3 (1.4)	3 (1.4)
Black or African American	11 (5.3)	14 (6.6)	8 (3.8)	13 (6.1)
White	197 (94.7)	193 (91.0)	197 (93.8)	196 (92.0)
Ethnicity, *n* (%), Hispanic/Latino[b]	11 (5.3)	11 (5.2)	9 (4.3)	15 (7.0)
Country, *n* (%), United States	188 (90.4)	192 (90.6)	182 (86.7)	186 (87.3)
APOE ε4 carrier, *n* (%)	133 (64.6)	136 (64.5)	137 (65.2)	137 (64.3)
ε4 homozygous, *n* (%)	21 (10.2)	21 (10.0)	22 (10.5)	21 (9.9)
Screening amyloid in Centiloids, mean (SD)	85.3 (36.6)	84.4 (37.6)	83.1 (35.3)	84.9 (39.4)
Microhemorrhage or cortical superficial siderosis, *n* (%)	50 (24.2)	55 (25.9)	44 (21.0)	49 (23.0)
MMSE, mean (SD)	24.6 (2.5)	25.1 (2.3)	24.7 (2.5)	24.5 (2.6)
Screening MMSE by clinical category				
Mild cognitive impairment (27–28), *n* (%)	59 (28.4)	73 (34.4)	69 (32.9)	57 (26.8)
Mild AD (20–26), *n* (%)	149 (71.6)	139 (65.6)	141 (67.1)	155 (72.8)
Time since onset of AD symptom, mean (SD), in years	3.8 (3.3)	3.9 (3.2)	4.1 (3.3)	3.8 (2.3)
AChEI and/or memantine use, *n* (%), yes	84 (40.4)	70 (33.0)	69 (32.9)	85 (39.9)

Abbreviations: AChEI, acetylcholinesterase inhibitor; AD, Alzheimer's disease; *APOE*, apolipoprotein E; C_{max}, maximum serum concentration; MMSE, Mini-Mental State Examination; *N*, number of participants in randomized population; *n*, number of participants per category; SD, standard deviation.

[a]The number of participants with non-missing data was used as the denominator.

[b]Only included responses from sites in the United States; *n* is the number of participants with a value of "Hispanic or Latino" or "Not Hispanic or Latino."

Cox proportional hazard analysis of time to first ARIA-E based on MRI showed a significantly ($P = 0.016$) lower percentage of participants with ARIA-E risk in the modified titration arm compared to the standard arm through 24 weeks (Figure 2B; 52-week data: Figure S2C).

When the impact of *APOE* ε4 genotypes was assessed, ARIA-E was numerically less frequent in the modified titration arm than in the standard arm regardless of genotype. The biggest difference (both relative and absolute) in ARIA-E frequency was observed in those homozygous for *APOE* ε4 (57.1% in the standard arm compared to 19.0% in the modified titration arm; Figure 3A, Figure S3A and Table S5; 52-week data: Figure S3B and Table S6). The frequency of symptomatic ARIA-E in homozygous, heterozygous, and non-carrier participants was 4.8%, 8.0%, and 0%, respectively, in the standard arm and 0%, 3.5%, and 2.7%, respectively, in the modified titration arm (Figure 3B and Figure S3C; 52-week data: Figure S3D).

3.3 | ARIA-H and macrohemorrhage

Compared to 25.1% of participants in the standard arm at 24 weeks, the modified titration arm resulted in 20.3% participants experiencing ARIA-H (Table 2 and Table S1; 52-week data: Table S3). The posterior probability that the RRR was ≥ 20% was 47.9% in the modified titration arm, which did not meet the predefined threshold of 80%. Consistent with the non-significant ARIA-H result, the frequency of microhemorrhage was not significantly different in the modified titration arm versus the standard arm. Cortical superficial siderosis, on the other hand, was significantly reduced in the modified titration arm compared to the standard arm with a 45% RRR and a 92.3% probability that the RRR was ≥ 20% (Table 2 and Table S2; 52-week data: Table S4). For ARIA-H events that were concurrent with ARIA-E (15.5% and 9.9% of events in the standard and modified titration arms, respectively), the modified titration arm also had a significantly lower relative risk (33.7%) and an 80.5% probability that the RRR was ≥ 20%. ARIA-H radiographic severities were not significantly different between the standard and modified titrations arms (Figure S4A; 52-week data: Figure S4B).

Macrohemorrhage occurred in one (0.5%) participant in the standard arm and two (0.9%) participants in the modified titration arm (Table 2 and Table S1; 52-week data: Table S3). By the primary outcome data lock date, one participant in the modified titration arm died due to cerebral hemorrhage, as discussed in the following section.

3.4 | Safety

One death occurred in an *APOE* ε4 heterozygous genotype participant in the modified treatment arm due to cerebral hemorrhage after

TABLE 2 ARIA through 24 weeks.

Category, n (%)	Standard (*N* = 207)	Modified titration (*N* = 212)	Modified titration versus standard arm			
			Posterior RRR (Posterior SD)	95% CrI RRR	Posterior probability of RRR ≥ 20%	Intercept prior was elicited as *N*
ARIA-E[a,b]	49 (23.7)	29 (13.7)	0.405 (0.123)	0.135, 0.616	**94.1***	(−1.49, 8.10)
Asymptomatic[a,b]	39 (18.8)	23 (10.8)				
Symptomatic[a,b]	10 (4.8)	6 (2.8)				
ARIA-H[a,c]	52 (25.1)	43 (20.3)	0.181 (0.145)	−0.138, 0.434	47.9	(−1.31, 8.55)
Asymptomatic[a,c]	52 (25.1)	42 (19.8)				
Symptomatic[a,c,d]	0 (0)	1 (0.5)				
Microhemorrhage[e]	41 (19.8)	36 (17.0)	0.128 (0.175)	−0.262, 0.421	36.7	(−1.59, 7.88)
Cortical superficial siderosis[e]	26 (12.6)	14 (6.6)	0.450 (0.168)	0.066, 0.711	**92.3***	(−2.34, 6.83)
Macrohemorrhages[a,f]	1 (0.5)	2 (0.9)				
SAE of macrohemmorrhage[g]	0 (0)	1 (0.5)				
Cerebral hemorrhage[g]	0 (0)	1 (0.5)				
Hemorrhagic stroke[g]	0 (0)	0 (0)				
Any ARIA (either E or H)[a,b,c]	67 (32.4)	50 (23.6)	0.261 (0.111)	0.023, 0.458	73.1	(−1.01, 9.55)
Any SAE of ARIA (either E or H)[g]	0 (0)	0 (0)				
Concurrent ARIA-E and ARIA-H[e]	32 (15.5)	21 (9.9)	0.337 (0.168)	−0.043, 0.608	**80.5***	(−2.18, 9.99)

Abbreviations: ARIA-E, amyloid-related imaging abnormalities with edema/effusions; ARIA-H, amyloid-related imaging abnormalities with hemorrhages/hemosiderin deposition; CrI, credible interval; MRI, magnetic resonance imaging; *N*, number of participants in the analysis population; *n*, number of participants within each specific category; RRR, relative risk reduction; SAE, serious adverse event; SD, standard deviation; TEAE, treatment-emergent adverse event.

*Bold text indicates significant difference.

[a]Based on MRI or TEAE cluster.

[b]ARIA-E TEAE cluster preferred terms are ARIA edema/effusion, brain edema, and vasogenic cerebral edema.

[c]ARIA-H TEAE cluster preferred terms are ARIA-microhemorrhage and hemosiderin deposits, brainstem microhemorrhage, cerebellar microhemorrhage, cerebral hemosiderin deposit, cerebral microhemorrhage, and cortical superficial siderosis of the central nervous system.

[d]Symptomatic ARIA-H low level term includes symptomatic ARIA-H, symptomatic ARIA-microhemorrhages and hemosiderin deposits, symptomatic ARIA-microhemorrhages and hemosiderin deposits, and symptomatic ARIA-cortical superficial siderosis.

[e]Based on MRI only.

[f]Macrohemorrhage preferred terms are cerebral hemorrhage and hemorrhagic stroke.

[g]Based on TEAE cluster.

thrombolytic administration for presumed acute right middle cerebral artery stroke. After receiving six doses of donanemab, ARIA-E of mild severity with six microhemorrhages in the right parietal lobe was detected on the scheduled week-24 MRI. Seven days after this MRI, the participant presented with seizures and left hemiparesis and was treated for presumed acute right middle cerebral artery stroke with hypodensity in the right parietal lobe on computerized tomography. The participant received intravenous tenecteplase (a tissue-type plasminogen activator treatment) as a treatment and died 2 days later due to a large cerebral hemorrhage. This highlights the label caution indicating ARIAs can mimic a stroke and thrombolytic treatment should be carefully considered.[2]

The frequency of serious adverse events was 8.7% in the standard arm and 9.9% in the modified titration arm. The frequency of treatment-emergent adverse events was similar in both arms (84.5% in the standard arm compared to 85.4% in the modified titration arm; Table 3 and Table S7; 52-week data: Table S8). The five most frequently reported treatment-emergent adverse events in either the standard or modified titration arm, respectively, were ARIA-E (23.7% and 13.7%), headache (19.8% and 15.1%), ARIA-H (15.9% and 13.2%), infusion-related reaction (13.5% and 17.0%), and fall (7.7% and 9.0%; Table 4 and Table S9; 52-week data: Table S10).

A total of 8 (3.9%) participants in the standard arm and 11 (5.2%) in the modified titration arm reported at least one adverse event as a reason for treatment discontinuation (Table 3 and Table S7; 52-week data: Table S8). The most common adverse event leading to treatment discontinuation was infusion-related reaction. Serious infusion-related reaction was reported in one (0.5%) participant in the standard arm and two (0.9%) participants in the modified titration arm by 24 weeks.

3.5 | Pharmacokinetics

The planned and observed cumulative doses, cumulative area under the curve $(AUC)_{(0\text{-}12\ weeks)}$ and $C_{average,ss}$ in the standard and modified titration arms were comparable. The overlapping distributions

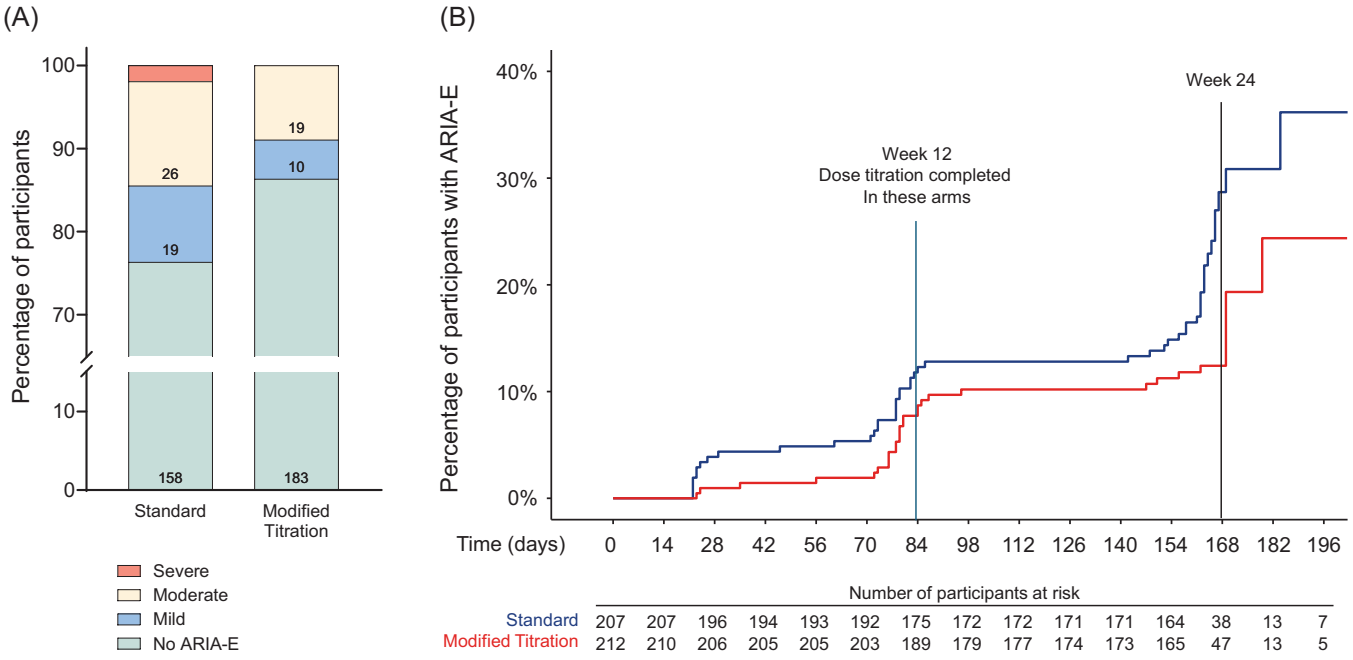

FIGURE 2 ARIA-E severity and time to first incidence through 24 weeks. A, ARIA-E maximum radiographic severity based on Cochran–Mantel–Haenszel test ($P = 0.011$). B, Kaplan–Meier curve showing hazard of time to first ARIA-E event based on MRI only. The percentage of participants with ARIA-E events is calculated using the number of participants who experienced ARIA-E by the given timepoint as the numerator and the number of participants still active in the study as the denominator. Participants at risk are the number of participants still active in the study and who have not yet experienced ARIA-E. Log-rank unstratified *P* value (2 sided) = 0.016. ARIA-E, amyloid-related imaging abnormalities with edema/effusions; MRI, magnetic resonance imaging

of cumulative $AUC_{(0\text{-}12\ weeks)}$ from individual participants on standard and modified titration are shown in Figure 4A and Table S11. Donanemab concentration-time profiles following standard and modified titration arms overlap completely after week 12, when the same once-monthly 1400 mg dosing regimen is used for both arms for the remainder of the study (Figure 4B).

3.6 | Pharmacodynamics and biomarkers

Participants had significant and highly comparable amyloid reduction from baseline to 24 weeks with an adjusted mean (standard error [SE]) change of 58.8 (1.8) CL in the standard arm, and 56.3 (1.7) CL in the modified titration arm (Figure 4C; 52-week data Figure S5A). Approximately 56.7% and 50.7% of participants in the standard regimen and modified titration regimen, respectively, reached an amyloid threshold level below 24.1 CL by week 24 (Table S12; 52-week data: Table S13). Approximately 33% of participants (32.3% in the modified titration arm; 34.0% in the standard arm) met the eligibility criteria for dose cessation at week 24 by achieving amyloid levels below 11 CL (Table S12; 52-week data: Table S13). Plasma p-tau217, assessed as an exploratory objective, was significantly reduced from baseline at 24 weeks and the reductions were similar in the standard and modified titration arms. The least squares mean change (log10) difference from baseline ± SE at week 24 was 0.136 ± 0.012 in the standard arm and 0.145 ± 0.012 in the modified titration arm ($P < 0.0001$; Figure 4D and Figure S5B).

4 | DISCUSSION

The primary endpoint for this study was ARIA-E frequency reduction at 24 weeks with an alternative donanemab dosing regimen compared to the standard donanemab dosing regimen and, therefore, that time point was the focus for this report. The modified titration arm had a lower frequency of ARIA-E (13.7%) compared to the standard arm (23.7%) and met the primary objective, with a 40.5% lower relative ARIA-E risk and a 94.1% probability that the RRR was ≥ 20%. Furthermore, the modified titration arm showed a significantly lower severity of ARIA-E and risk of cortical superficial siderosis compared to the standard arm. Importantly, the standard and modified titration arms had a similar amyloid reduction from baseline as assessed by PET scans (adjusted mean change at 24 weeks: 58.8 CL vs. 56.3 CL, respectively). The standard arm and modified titration arms also had similar cumulative exposure and plasma p-tau217 response.

The 52-week results were consistent with the 24-week results suggesting that ARIA-E was reduced rather than delayed in the modified titration arm. In addition, the amyloid reduction remained similar between the standard and the modified titration arms at week 52 (adjusted mean change at 52 weeks: 71.2 CL vs. 70.3 CL, respectively).

Previous trials with amyloid-targeting therapies have suggested that not only is the frequency of ARIA dose dependent, but also that the risk of ARIA can be reduced by implementing titration.[7,15–17] Additionally, it has been hypothesized that ARIA might be C_{max} dependent, however lecanemab data did not support this observation.[18,19]

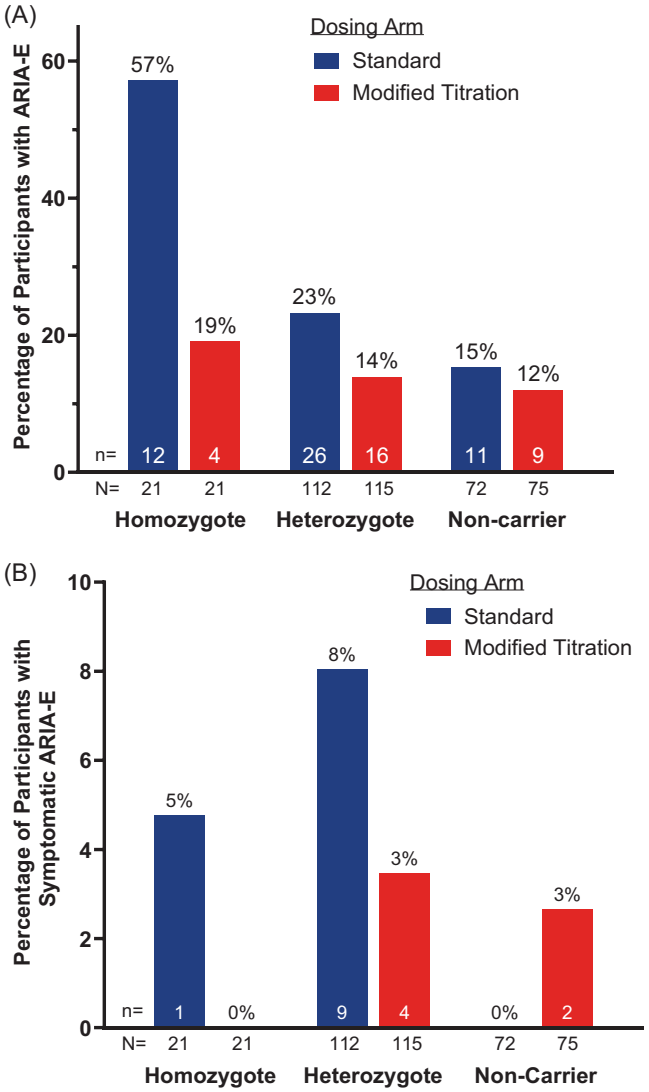

FIGURE 3 ARIA-E by *APOE* ε4 genotype. Post hoc analyses based on safety MRI. Bar graphs show (A) the frequency of ARIA-E by *APOE* ε4 genotype and (B) symptomatic ARIA-E by *APOE* ε4 genotype. *APOE*, apolipoprotein E; ARIA-E, amyloid-related imaging abnormalities with edema/effusions; MRI, magnetic resonance imaging

To achieve the goal of reducing ARIA-E frequency while maintaining comparable amyloid reduction, the rational design and selection of the alternative dosing regimens in this study were based on human safety, efficacy, pharmacokinetic, and pharmacodynamic data from donanemab phase 1 through 3 studies. All dosing regimens were expected to result in robust amyloid plaque reduction. The comparable cumulative exposure and the pharmacodynamic effect observed between the standard and modified titration arms validated the dosing regimen selection. The modified titration arm dosing differed from the standard arm simply by the timing of a single vial (350 mg), which was removed from the first infusion and added to the third infusion.

The randomization and stratification approaches in this study were designed to balance ARIA risk factors; thus, *APOE* ε4 genotype, baseline amyloid levels, baseline microhemorrhage, and cortical superficial siderosis were equal across arms. As a result, the standard arm provides a reliable internal comparison for the alternative dosing arms.

While the modified titration dosing regimen significantly reduced the relative ARIA-E risk there was no significant reduction in ARIA-H risk, although it was numerically lower. One possible reason for this finding is that the study was not powered to find a significant

TABLE 3 Safety overview through 24 weeks.

Category[a], n (%)	Standard (*N* = 207)	Modified titration (*N* = 212)
Deaths[b]	0 (0)	1 (0.5)
Serious adverse events	18 (8.7)	21 (9.9)
SAE of ARIA-E[c]	0 (0)	0 (0)
Discontinuations from study due to an adverse event	4 (1.9)	5 (2.4)
Discontinuations from study treatment due to an adverse event	8 (3.9)	11 (5.2)
Treatment-emergent adverse events	175 (84.5)	181 (85.4)
Treatment-emergent adverse events related to study treatment[c]	104 (50.2)	103 (48.6)

Abbreviations: ARIA-E, amyloid-related imaging abnormalities with edema/effusions; *N*, number of participants in the analysis population; *n*, number of participants with at least one adverse event per event type; SAE, serious adverse events; TEAE, treatment-emergent adverse events.
[a]Participants may be counted in more than one category.
[b]Deaths are also included as serious adverse events and discontinuations due to adverse events.
[c]Includes events that were considered related to study treatment as judged by the investigator.

TABLE 4 Treatment-emergent adverse events occurring in ≥ 5% of participants in standard or modified titration arm through 24 weeks.

Preferred term, *n* (%)	Standard (*N* = 207)	Modified titration (*N* = 212)
Participants with ≥ 1 TEAE	175 (84.5)	181 (85.4)
Amyloid-related imaging abnormality-edema/effusion	49 (23.7)	29 (13.7)
Headache	41 (19.8)	32 (15.1)
Amyloid-related imaging abnormality-hemorrhages and hemosiderin deposits	33 (15.9)	28 (13.2)
Infusion-related reaction	28 (13.5)	36 (17.0)
Fall	16 (7.7)	19 (9.0)
Dizziness	19 (9.2)	17 (8.0)
COVID-19	10 (4.8)	19 (9.0)
Urinary tract infection	7 (3.4)	16 (7.5)
Diarrhea	12 (5.8)	6 (2.8)
Fatigue	11 (5.3)	12 (5.7)
Cortical superficial siderosis of central nervous system	12 (5.8)	5 (2.4)
Arthralgia	8 (3.9)	13 (6.1)

Abbreviations: COVID-19, coronavirus disease 2019; *N*, number of participants in the analysis population; *n*, number of participants within each specific category; TEAE, treatment-emergent adverse event.

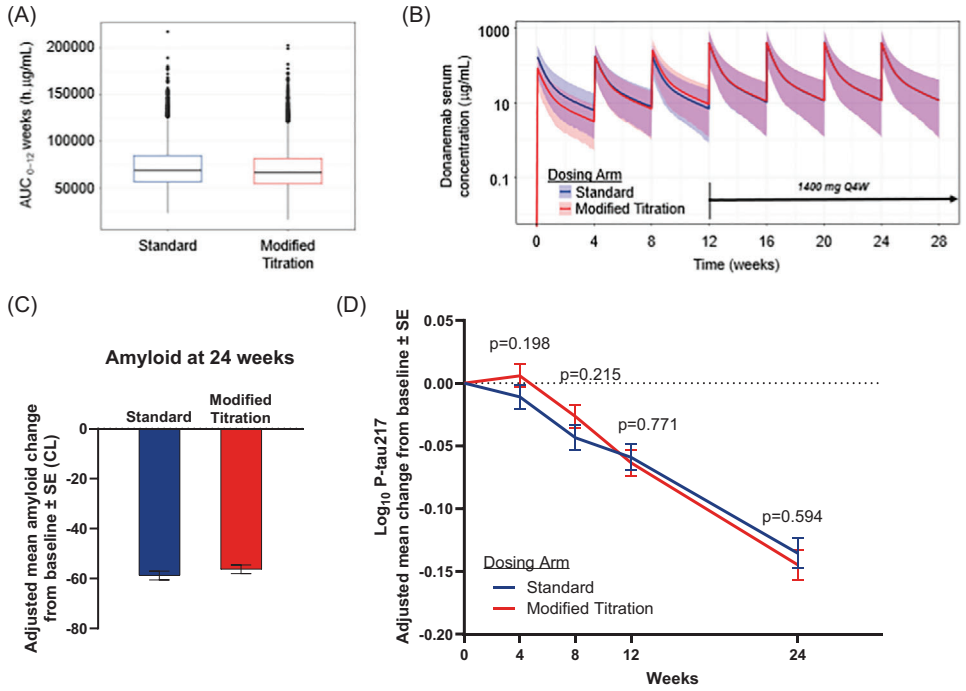

FIGURE 4 Pharmacokinetics and biomarkers. A, Observed cumulative exposure $AUC_{(0\text{-}12\ weeks)}$ from standard and modified titration arms. B, Donanemab concentration-time profiles. Solid line: median of serum concentrations; shaded areas: 90% prediction intervals (including between-participant and residual error). Population pharmacokinetic methodology was used. C, Reduction in amyloid levels after 24 weeks. The ANCOVA model was used for 24-week values with the following variables: baseline amyloid (in CL) + dosing regimen + baseline age. ANOVA was used for baseline measures with dosing regimen as the variable. D, Plasma p-tau217 as assessed on Eli Lilly and Company's Meso Scale Discovery platform using the mixed model for repeated measures with an unstructured variance-covariance. ANCOVA, analysis of covariance; ANOVA, analysis of variance; AUC, area under the curve; CL, Centiloid; *n*, number of participants within each specific category; p-tau, phosphorylated tau; Q4W, every 4 weeks; SE, standard error

lowering of ARIA-H given that it commonly occurs spontaneously (in TRAILBLAZER-ALZ 2, 13.6% of placebo-treated participants experienced ARIA-H).[5] Most ARIA-H resulting from amyloid-targeting therapies co-occurs with ARIA-E and there is generally no difference between placebo and amyloid-targeting therapies for isolated ARIA-H.[20,21] Assuming this pattern is maintained, a larger study would be needed to detect significant overall lowering of ARIA-H. Consistent with this hypothesis, for ARIA-H events that are concurrent with ARIA-E, which are mostly treatment induced, the modified titration regimen demonstrated significantly reduced risk, with > 80% probability of achieving at least 20% RRR.

The mechanistic basis behind the lower ARIA-E frequency in the modified titration arm is yet to be determined. A possible mechanism is that the initial lower dose reduces binding of the antibody to vascular amyloid resulting in slower removal of vascular amyloid with less leakiness and inflammation. A second potential explanation is that the slower increase in serum donanemab concentration might result in more gradual mobilization of amyloid via the perivascular spaces, thus limiting exacerbation of cerebral amyloid angiopathy.[22] These two candidate mechanisms are not mutually exclusive and could both contribute to the observed reduction in ARIA risk.

Infusion-related reaction frequency observed in this study was higher than that previously reported with donanemab treatment (13.5% in the standard arm vs. 8.7% in TRAILBLAZER-ALZ 2).[5] The standard arm in this study differed from the donanemab arm in TRAILBLAZER-ALZ 2 as the standard arm incorporated additional placebo infusions to maintain the study blind (C_{max} dosing was bi-weekly for the first 16 weeks). This bi-weekly infusion schedule, as opposed to once monthly, as well as the participants' awareness of receiving donanemab as opposed to blinded placebo-controlled trials, might have influenced the observed infusion-related reaction frequency.

In interpreting these results, it is important to consider that the TRAILBLAZER-ALZ 6 study is ongoing at the time of this report, with only data through 52 weeks available. Nevertheless, in previous donanemab trials, nearly 90% of ARIA-E events occurred within the first 24 weeks.[2,4,5] Continued monitoring and dosing through 18 months in TRAILBLAZER-ALZ 6 will further confirm the findings reported here. Another limitation is that the study size restricts the ability to detect significant differences in small subgroups or less frequent safety events. Although not powered to detect differences within *APOE* ε4 genotypes, post hoc Bayesian logistic regression analyses showed more than an 80% posterior probability of achieving at least a 20% RRR in ARIA-E frequency across all *APOE* ε4 genotypes in the modified titration arm compared to the standard arm. Furthermore, the study was conducted in two countries, representing a smaller geographic scope than TRAILBLAZER-ALZ 2. In addition, TRAILBLAZER-ALZ 6 was designed as a safety study and

clinical changes (in cognition and function) were not assessed. However, cumulative dose, cumulative exposure, and pharmacodynamic measures of amyloid lowering and p-tau217 lowering were similar between the standard arm (as used in TRAILBLAZER-ALZ 2) and all three alternative dosing arms. This supports pharmacokinetic- and pharmacodynamic-based bridging to clinical efficacy, as presented in guidance from the US Food and Drug Administration.[23,24] Amyloid reduction is an acceptable surrogate biomarker for clinical outcomes in AD.[23,24]

TRAILBLAZER-ALZ 6 aims to expand the science and understanding of ARIAs in relationship to amyloid lowering, with the goal of maximizing the benefits and lowering the risks of amyloid-targeting therapies for patients with early symptomatic AD. The primary endpoint at week 24 showed that modified titration of donanemab can decrease the frequency of ARIAs without impacting amyloid removal. At the time of this report, the estimated last participant visit is projected for mid-2025.

ACKNOWLEDGMENTS

The authors thank the participants, caregivers, and investigators. The authors would also like to thank Wen Xu (Eli Lilly and Company) for her contributions as lead statistician for the 52-week data and Raena Fernandes and Antonia Baldo (Syneos Health) for editorial assistance. This study was funded by Eli Lilly and Company. The data from this study were presented in part at the 17th Clinical Trials on Alzheimer's Disease (CTAD), October 29 to November 1, 2024, in Madrid, Spain.

CONFLICT OF INTEREST STATEMENT

HW, ESMN, PA, RK, DOS, IG, SS-Eli Lilly and Company, SWA, PMH, SEE, DAB, ECC, MAM, and JRS are employees and minor shareholders of Eli Lilly and Company. NCF reports consulting fees from Biogen, Eisai, Eli Lilly, and Roche (all paid to UCL); he has received fees for serving on a data safety monitoring board for Biogen and on an advisory board for Abbvie; acknowledges grant support from the Alzheimer's Society (UK), Alzheimer's Research UK, Rosetrees Trust, the Sigrid Rausing Trust, and the UK NIHR UCLH Biomedical Research Centre. SMG reports receiving consulting fees from Eli Lilly and Company and participates in safety data monitoring boards or advisory boards for IQVIA/Washington University. SS-Butler Hospital receives research support for conducting clinical trials through grants or contracts from Biogen, Eisai, Genentech, Roche, CognitionRx, Lilly, and Janssen; he has received consulting fees from Abbvie, Acumen, Alector, Biogen, Biohaven, Cognition, Eisai, Fujirebio, Genentech, Kisbee, Laqbcorp, Lilly, Merck, Neurophet, NovoNordisk, Prothena, Quest, and Roche. Author disclosures are available in the supporting information.

CONSENT STATEMENT

All patients gave informed consent for participation in the study prior to any study-specific procedures.

REFERENCES

1. Gustavsson A, Norton N, Fast T, et al. Global estimates on the number of persons across the Alzheimer's disease continuum. *Alzheimers Dement*. 2023;19(2):658-670.
2. *Kisunla (donaneamb-azbt) [product insert]*. 2024. Eli Lilly and Company.
3. *Leqembi (lecanemab-irmb) [package insert]*. 2023. Eisai Inc.
4. Mintun MA, Lo AC, Duggan Evans C, et al. Donanemab in early Alzheimer's disease. *N Engl J Med*. 2021;384(18):1691-1704.
5. Sims JR, Zimmer JA, Evans CD, et al. Donanemab in early symptomatic Alzheimer disease: the TRAILBLAZER-ALZ 2 randomized clinical trial. *JAMA*. 2023;330(6):512-527.
6. van Dyck CH, Swanson CJ, Aisen P, et al. Lecanemab in early Alzheimer's disease. *N Engl J Med*. 2023;388(1):9-21.
7. Budd Haeberlein S, Aisen PS, Barkhof F, et al. Two randomized phase 3 studies of aducanumab in early Alzheimer's disease. *J Prev Alzheimers Dis*. 2022;9(2):197-210.
8. Salloway S, Honigberg LA, Cho W, et al. Amyloid positron emission tomography and cerebrospinal fluid results from a crenezumab anti-amyloid-beta antibody double-blind, placebo-controlled, randomized phase II study in mild-to-moderate Alzheimer's disease (BLAZE). *Alzheimers Res Ther*. 2018;10(1):96.
9. Barakos J, Purcell D, Suhy J, et al. Detection and management of amyloid-related imaging abnormalities in patients with Alzheimer's disease treated with anti-amyloid beta therapy. *J Prev Alzheimers Dis*. 2022;9(2):211-220.
10. Arrighi HM, Barakos J, Barkhof F, et al. Amyloid-related imaging abnormalities-haemosiderin (ARIA-H) in patients with Alzheimer's disease treated with bapineuzumab: a historical, prospective secondary analysis. *J Neurol Neurosurg Psychiatry*. 2016;87(1):106-112.
11. Sims JR, Iwatsubo T, Greenberg SM, Mintun M, Atri A, Zimmer JA. Brooks S2- Donanemab in early symptomatic Alzheimer's disease: additional insights from TRAILBLAZER-ALZ. From: 16th Clinical Trials on Alzheimer's Disease (CTAD) Boston, MA (USA) October 24-27, 2023. *J Prev Alzheimers Dis*. 2023;10:4-55.
12. Fazekas F, Chawluk JB, Alavi A, Hurtig HI, Zimmerman RA. MR signal abnormalities at 1.5 T in Alzheimer's dementia and normal aging. *AJR Am J Roentgenol*. 1987;149(2):351-356.
13. Rissman RA, Donohue MC, Langford O, et al. Longitudinal phospho-tau217 predicts amyloid positron emission tomography in asymptomatic Alzheimer's disease. *J Prev Alzheimers Dis*. 2024;11(4):823-830.
14. Wang YC, Ji P, Hariharan S, et al. Clinical pharmacology approaches to support approval of new routes of administration for therapeutic proteins. *Clin Pharmacoly Ther*. 2024;115(3):440-451.
15. Bateman RJ, Smith J, Donohue MC, et al. Two phase 3 trials of gantenerumab in early Alzheimer's disease. *N Engl J Med*. 2023;389(20):1862-1876.
16. Retout S, Gieschke R, Serafin D, Weber C, Frey N, Hofmann C. Disease modeling and model-based meta-analyses to define a new direction for a phase III program of gantenerumab in Alzheimer's disease. *Clin Pharmacol Ther*. 2022;111(4):857-866.
17. Sevigny J, Chiao P, Bussière T, et al. The antibody aducanumab reduces Aβ plaques in Alzheimer's disease. *Nature*. 2016;537(7618):50-56.
18. Van Dyck C, Johnson K, Sperling R, Irizarry M. S4-Lecanemab for early Alzheimer's disease: long-term outcomes, predictive biomarkers and novel subcutaneous administration. From: 16th Clinical Trials on Alzheimer's Disease (CTAD) Boston, MA (USA) October 24-27, 2023. *J Prev Alzheimers Dis*. 2023;10(1):4-55.
19. Majid O, Cao Y, Willis BA, et al. Population pharmacokinetics and exposure-response analyses of safety (ARIA-E and isolated ARIA-H) of lecanemab in subjects with early Alzheimer's disease. *CPT: Pharmacometrics & Syst Pharmacol*. 2024;13(12):2111-2123. doi:10.1002/psp4.13224
20. Mintun M, Ritchie CW, Solomon P, et al. Donanemab in early symptomatic Alzheimer's disease: efficacy and safety in TRAILBLAZER-ALZ 2, a phase 3 randomized clinical trial. *Alzheimers Dement*. 2023;19(S24):e082733.

21. Honig LS, Sabbagh MN, van Dyck CH, et al. Updated safety results from phase 3 lecanemab study in early Alzheimer's disease. *Alzheimers Res Ther*. 2024;16(1):105.
22. Greenberg SM, Bacskai BJ, Hernandez-Guillamon M, Pruzin J, Sperling R, van Veluw SJ. Cerebral amyloid angiopathy and Alzheimer disease—one peptide, two pathways. *Nat Rev Neurol*. 2020;16(1):30-42.
23. Wang G, Li Y, Xiong C, et al. Examining amyloid reduction as a surrogate endpoint through latent class analysis using clinical trial data for dominantly inherited Alzheimer's disease. *Alzheimers Dement*. 2024;20(4):2698-2706.
24. [FDA] Food and Drug Administration. Early Alzheimer's disease: developing drugs for treatment. Guidance for Industry. Draft guidance. 2024. Accessed 3 December, 2024. https://www.fda.gov/media/110903/download

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Wang H, Serap Monkul Nery E, Ardayfio P, et al. Modified titration of donanemab reduces ARIA risk and maintains amyloid reduction. *Alzheimer's Dement*. 2025;21:e70062. https://doi.org/10.1002/alz.70062