The Effect of Different Donanemab Dosing Regimens on ARIA-E and Amyloid Lowering in Adults with Early Symptomatic Alzheimer's Disease: Primary Outcome Results from TRAILBLAZER-ALZ 6

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OBJECTIVE

TRAILBLAZER-ALZ 6 was designed to increase understanding of ARIA

- Amyloid-related imaging abnormalities (ARIA) have been observed with amyloid-targeting therapies, including donanemab.
- TRAILBLAZER-ALZ 6 (NCT05738486) assesses the impact of different donanemab dosing options on the frequency of ARIA-E in relation to amyloid reduction.
- Focus on inclusion of a modified titration starting at 350 mg (AUC-based rationale)
- Also included a dosing regimen to inform AD field on AUC vs Cmax drivers for ARIA.

SUMMARY

- Based on 24-week data, a change in the initiation of donanemab dosing, shifting one vial from the first infusion to the third infusion (the modified titration arm) resulted in:
  - significantly lower ARIA-E (14%), compared to 24% in currently approved dosing schedule (standard arm)
    - lower symptomatic ARIA-E (2.8%) versus standard arm (4.8%)
    - lower radiographic severity across categories of ARIA-E
    - lower ARIA-E (19%) in APOE ε4/4 versus standard arm (57%)
  - comparable pharmacokinetic profile
  - comparable amyloid and P-tau217 lowering

- Trial is still ongoing (12- and 18-month endpoints)
- Considering potential implications for HCPs and patients, Lilly plans to engage global regulators for possible updates to labels

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ABSTRACT

Introduction: Donanemab is a monoclonal antibody specific for an insoluble form of amyloid beta present only in brain amyloid plaques. Donanemab has been approved-for treatment of Alzheimer's disease (AD). Amyloid-related imaging abnormalities (ARIA) have been observed with amyloid-targeting therapies, including donanemab. TRAILBLAZER-ALZ 6 (NCT05738486) assessed the impact of different donanemab dosing regimens on the frequency of ARIA-E in relation to amyloid reduction.

Methods: This was a multicenter, randomized, double-blind, phase 3b study in adults with early symptomatic AD and presence of amyloid pathology. Participants (n=843) were stratified by *APOE* genotype and baseline amyloid levels and randomly assigned to the standard dosing arm or one of 3 alternative dosing arms in a 1:1:1:1 ratio. 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. Relative risk reduction of ARIA-E by week 24 was analyzed through Bayesian logistic regression models to compare each alternate dosing regimen with the standard dosing approach. Brain amyloid level (as measured by positron emission tomography) and plasma P-tau217 level were also assessed.

Results: By week 24, the frequency of ARIA-E was 23.7% for the standard dosing arm, and 18.6%, 13.7%, and 18.3% for the 3 alternative dosing arms. The modified titration dosing regimen with the lowest ARIA-E (13.7%) had a 41% reduction in the relative risk of ARIA-E compared to the standard dosing arm. The ARIA-E radiographic severity in the modified titration arm was significantly less than the standard dosing arm with 4.7%, 9.0%, and 0% of mild, moderate and severe ARIA-E compared to 9.2%, 12.6% and 1.9%, respectively, in the standard dosing arm. The symptomatic ARIA-E frequency was 2.8% in the modified titration arm compared to 4.8% in the standard arm. Serious adverse events, discontinuations or treatment-related adverse events in the alternative dosing arms were largely comparable to the standard dosing arm. One participant in the titration arm with an ongoing ARIA-E presented stroke-like symptoms and, after receiving tissue plasminogen activator treatment, subsequently died due to cerebral intraparenchymal hemorrhage. The frequencies of infusion-related reactions in the alternative dosing arms were similar to the standard arm. Participants in all arms had significant amyloid reduction from baseline to 24 weeks with adjusted mean (SE) change of 58.8 (1.8) Centiloids in the standard arm, 56.3 (1.7) in the modified titration arm, and 58.7 (1.7), and 51.0 (1.7) Centiloids in the other alternative dosing arms. Plasma P-tau217 reductions at 24 weeks were similar in all dosing arms as well.

Conclusions: The frequency and severity of ARIA-E at 24 weeks was significantly reduced in the modified titration arm and numerically lower in the other two dosing arms compared to the standard arm. Amyloid and plasma P-tau217 reduction was similar in the standard and modified titration arm. This study suggests that a modified titration approach may limit ARIA risk while maintaining sufficient amyloid reduction.

STUDY DESIGN

1:1:1:1 Randomization stratified by *APOE* and by baseline amyloid PET

Cumulative donanemab exposure was the same for the 4 dosing regimens by week 16.

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
Treatment Arm (mg): 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	√			√			√					√

Placebo was given at the indicated visits to preserve the blind for the different dosing regimens.

After week 16, all participants received 1400 mg of donanemab monthly until dose stopping criteria was met or until the end of the study.

350 mg = 700 mg = 1050 mg = 1400 mg =

KEY RESULT

Modified titration arm met primary objective (significant lowering of ARIA-E)

- Primary objective: Posterior probability of alternative arm achieving at least 20% relative risk reduction (RRR) versus standard arm is more than 80%.
- ARIA-E frequency was significantly reduced in the modified titration arm compared to the standard dosing arm (Posterior Probability of RRR ≥20% = 94%)

	Standard (N=207)	Modified Titration (N=212)	Dose Skipping (N=210)	Cmax (N=213)
ARIA-E [a], n (%)	49 (23.7)	29 (13.7)	39 (18.6)	39 (18.3)
Bayesian logistic regression model versus standard arm				
Posterior RRR (Posterior SD)		0.405 (0.123)	0.195 (0.146)	0.211 (0.145)
95% Credible Interval RRR		0.135, 0.616	-0.130, 0.447	-0.097, 0.465
Posterior Probability of RRR ≥20%		**94.1%**	51.2%	56.6%

[a] Based on MRI or TEAE cluster preferred terms are ARIA oedema/effusion, brain oedema, and vasogenic cerebral oedema

Baseline Characteristics

Category	Standard (N=208)	Modified Titration (N=212)	Dose Skipping (N=210)	Cmax (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	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 centiloid, mean (SD)	85.3 (36.6)	84.4 (37.6)	83.1 (35.3)	84.9 (39.4)
Microhemorrhage or superficial siderosis, n (%), yes	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)

Denominator of percentage calculation is the number of participants with non-missing data.

ARIA frequencies by 24 weeks

	Standard (N=207) n (%)	Modified Titration (N=212) n (%)
Any ARIA (either E or H) [a,b,c], n (%)	67 (32.4)	50 (23.6)
Concurrent ARIA-E and ARIA-H [d]	32 (15.5)	21 (9.9)
ARIA-E [a,b], n (%)	49 (23.7)	29 (13.7)
Symptomatic [a,b,*], n (%)	10 (4.8)	6 (2.8)
ARIA-H [a,c], n (%)	52 (25.1)	43 (20.3)
Symptomatic [a,c,e], n (%)	0 (0)	1 (0.5)
Microhemorrhage [d], n (%)	41 (19.8)	36 (17.0)
Superficial siderosis [d], n (%)	26 (12.6)	14 (6.6)
Macrohemorrhages [a,f], n (%)	1 (0.5)	2 (0.9)

* Commonly reported symptoms of symptomatic ARIA-E were headache and confusion. [a] Based on MRI or TEAE cluster. [b] ARIA-E TEAE cluster preferred terms are: ARIA - oedema/effusion; brain oedema; vasogenic cerebral oedema. [c] ARIA-H TEAE cluster preferred terms are: ARIA - microhemorrhage and hemosiderin deposits; brainstem microhemorrhage; cerebellar microhemorrhage; cerebral hemosiderin deposit; cerebral microhemorrhage; and superficial siderosis of the central nervous system. [d] Based on MRI only. [e] Symptomatic ARIA-H Low Level Term includes symptomatic ARIA-H, symptomatic ARIA-microhemorrhages and haemosiderin deposits, symptomatic ARIA-microhemorrhages and hemosiderin deposits, and symptomatic ARIA-superficial siderosis. [f] Macrohemorrhage preferred term are cerebral hemorrhage; and hemorrhagic stroke.

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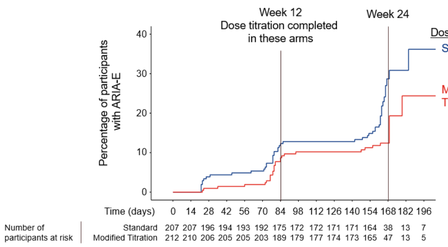
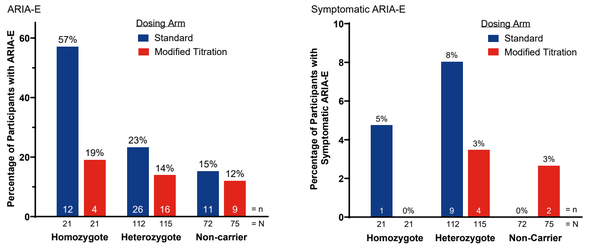
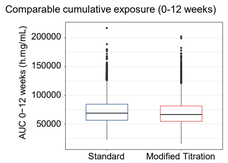
Significantly lower ARIA-E risk over time in the modified titration arm (p-value* = 0.016)

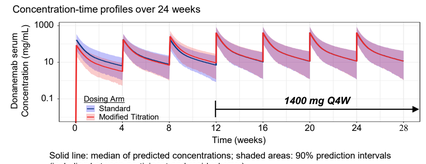


Reduction of ARIA-E and symptomatic ARIA-E across APOE ε4 genotypes in the modified titration arm



Comparable cumulative exposure in the modified titration and standard dosing arms

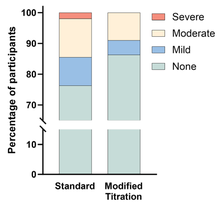




Solid line: median of predicted concentrations; shaded areas: 90% prediction intervals (including between-participant and residual error).

Observed individual participant AUC 0-12 weeks (8 samples per participant, N: ~200 per arm): population pharmacokinetic method to estimate serum exposure

Reduced ARIA-E maximum radiographic severity in the modified titration arm



- ARIA-E severity distribution is significantly shifted toward none or less severe direction in the modified titration arm with p=0.011 (Cochran-Mantel-Haenszel test)
- **86% of participants in the modified titration arm have no ARIA-E by MRI through Week 24**

Safety Overview

Category [a]	Standard (N=207)	Modified Titration (N=212)
Deaths [b], n (%)	0	1 (0.5)
Serious Adverse Events, n (%)	18 (8.7)	21 (9.9)
Discontinuations from Study due to an AE, n (%)	4 (1.9)	5 (2.4)
Discontinuations from Study Treatment due to an AE, n (%)	8 (3.9)	11 (5.2)
TEAE's, n (%)	175 (84.5)	181 (85.4)
TEAE's Related to Study Treatment [c], n (%)	104 (50.2)	103 (48.6)

TEAE ≥ 10%

Category	Standard (N=207)	Modified Titration (N=212)
Participants with ≥1 TEAE, n (%)	175 (84.5)	181 (85.4)
Amyloid related imaging abnormality-oedema/effusion, n (%)	49 (23.7)	29 (13.7)
Headache, n (%)	41 (19.8)	32 (15.1)
Amyloid related imaging abnormality-microhaemorrhages and haemosiderin deposits, n (%)	33 (15.9)	28 (13.2)
Infusion-related reaction, n (%)	28 (13.5)	36 (17.0)

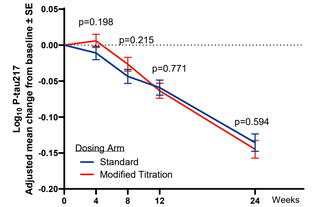
Note: MedDRA Version 27.0

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. One death occurred in the modified treatment arm due to cerebral hemorrhage following thrombolytic administration for presumed acute right middle cerebral artery (MCA) stroke. The participant had an *APOE* ε4 heterozygous genotype. After receiving 6 doses of donanemab, ARIA-E of mild severity with 6 microhemorrhages in the right parietal lobe was detected on Week 24 MRI. Seven days after the MRI which detected ARIA, the participant presented with left hemiparesis (seizure-like activity) and was treated for presumed acute right MCA stroke with hypodensity in right parietal lobe on computerized tomography. The patient received intravenous tenecteplase as a treatment and died 2 days later due to cerebral hemorrhage.
c - Includes events that were considered related to study treatment as judged by the investigator.

Comparable lowering of amyloid and P-tau217 over 24 weeks with standard dosing and modified titration

	Standard	Modified Titration
Mean baseline values, CL (SD)	84.9 (37.4)	83.7 (37.7)
Adjusted mean change from baseline*, CL (SE)	-58.8 (1.8)	-56.3 (1.7)
Percent reduction from baseline	69%	67%
Amyloid below 24.1 CL at 24 weeks, n (%)	110 (56.7)	102 (50.7)
Dose stopping criteria met (<11 CL), n (%)	66 (34.0)	65 (32.3)

Note: includes scheduled and unscheduled amyloid PET results.
* The ANCOVA model is: postbaseline amyloid Centiloid = baseline amyloid Centiloid + dosing regimen + baseline age.



As assessed on Eli Lilly and Company's Meso Scale Discovery platform by Mixed Model Repeated Measures with an unstructured variance-covariance.

Abbreviations: AChEI: acetyl-cholinesterase-inhibitor; AD: Alzheimer's disease; AE: adverse event; ANCOVA: analysis of covariance; ARIA-E=amyloid-related imaging abnormalities edema; *APOE*: apolipoprotein E; AUC: area under the curve; CL: Centiloid; COVID-19: Coronavirus Disease 2019; MMSE: Mini-Mental State Examination; MRI, magnetic resonance imaging; PET: positron emission tomography; N: number of participants in the analysis population; n: number of participants within each specific category; Q4W: every 4 weeks; RRR=relative risk reduction; SAE: serious adverse event; SD: standard deviation; SE: standard error; TEAE: treatment-emergent adverse events