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

Hong Wang, Emel Serap Monkul Nery, Paul Ardayfio, Rashna Khanna, Diana Otero Svaldi, Ivelina Gueorguieva, Sergey Shcherbinin, Scott W. Andersen, Paula M. Hauck, Dawn A. Brooks, Emily C. Collins, Mark A. Mintun, and John R. Sims

Eli Lilly and Company, Indianapolis, USA

Lilly

Presenter Disclosure and Acknowledgements

John Sims is an employee and minor shareholder of Eli Lilly and Company

We gratefully acknowledge the contribution and dedication of all the trial participants with AD, their families, and their caregivers who participated in this study, along with trial site investigators and personnel, and members of the data monitoring committee.

We also are appreciative of the advice and guidance provided by Stephen Salloway, Steven Greenberg, and Nick Fox on this study.

Scan the QR code or use this URL
https://lillyscience.lilly.com/congress/ctad2024
for a list of all Lilly content presented at the congress

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

TRAILBLAZER-ALZ 6 Study Design

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

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	√			√				√				√

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

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.

APOE: apolipoprotein E; MRI, magnetic resonance imaging; PET: positron emission tomography

Modified titration differs from standard dosing by timing change of a single vial

Dose	1	2	3	4	5	6	7
Study Week	0	4	8	12	16	20	24
Standard							
Modified Titration							

 =350 mg

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)

AChEI: acetyl-cholinesterase-inhibitor; AD: Alzheimer's disease; *APOE*: apolipoprotein E; MMSE: Mini-Mental State Examination; N: number of participants in randomized population; n: number of participants per category; SD: standard deviation.
Denominator of percentage calculation is the number of participants with non-missing data.

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%)

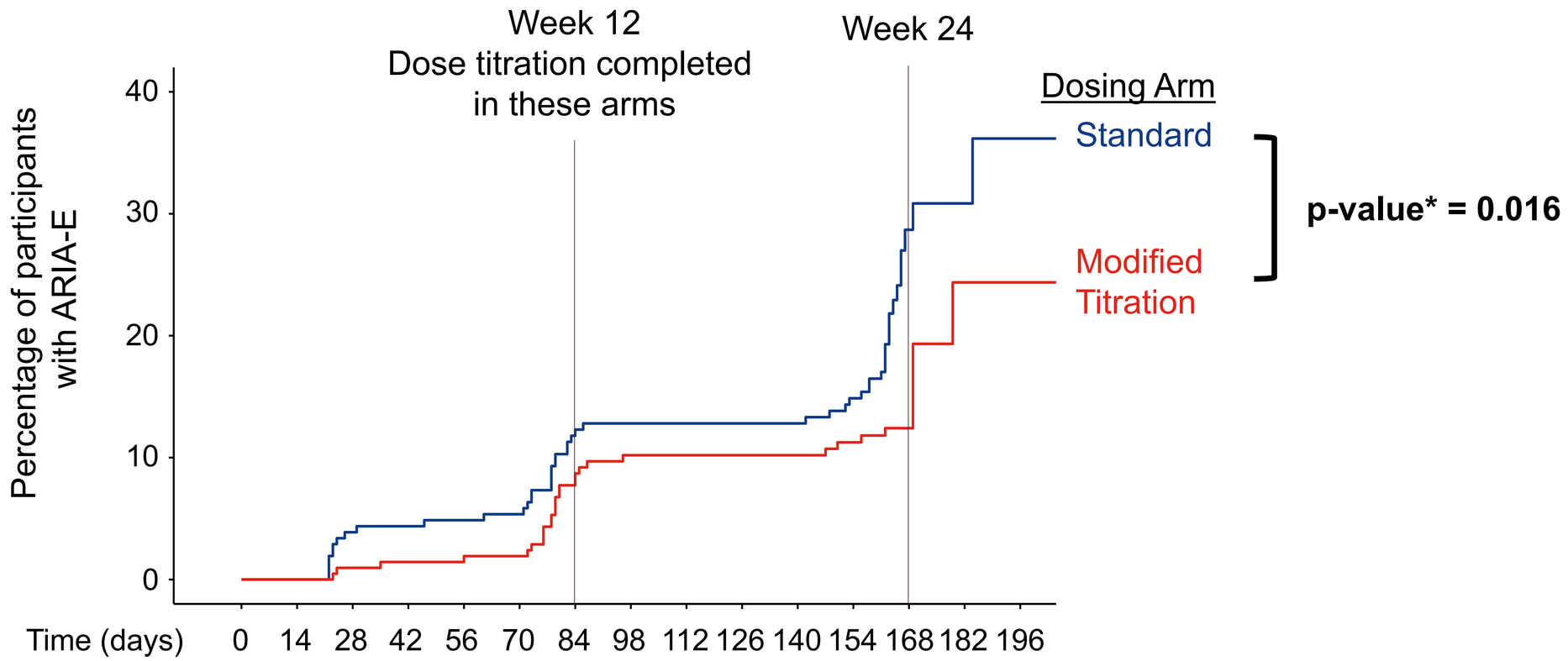
	Standard (N=207)	Modified Titration (N=212)	Dose Skipping (N=210)	Cmax (N=213)
ARIA-E [a], n (%)	49 (23.7)	29 (13.7)	39 (18.6)	39 (18.3)
Bayesian logistic regression model versus standard arm				
Posterior RRR (Posterior SD)		0.405 (0.123)	0.195 (0.146)	0.211 (0.145)
95% Credible Interval RRR		0.135, 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. ARIA-E TEAE cluster preferred terms are ARIA oedema/effusion, brain oedema, and vasogenic cerebral oedema

Abbreviations: ARIA-E=amyloid-related imaging abnormalities edema; MRI=magnetic resonance imaging; RRR=relative risk reduction; SD=standard deviation; TEAE= treatment-emergent adverse events

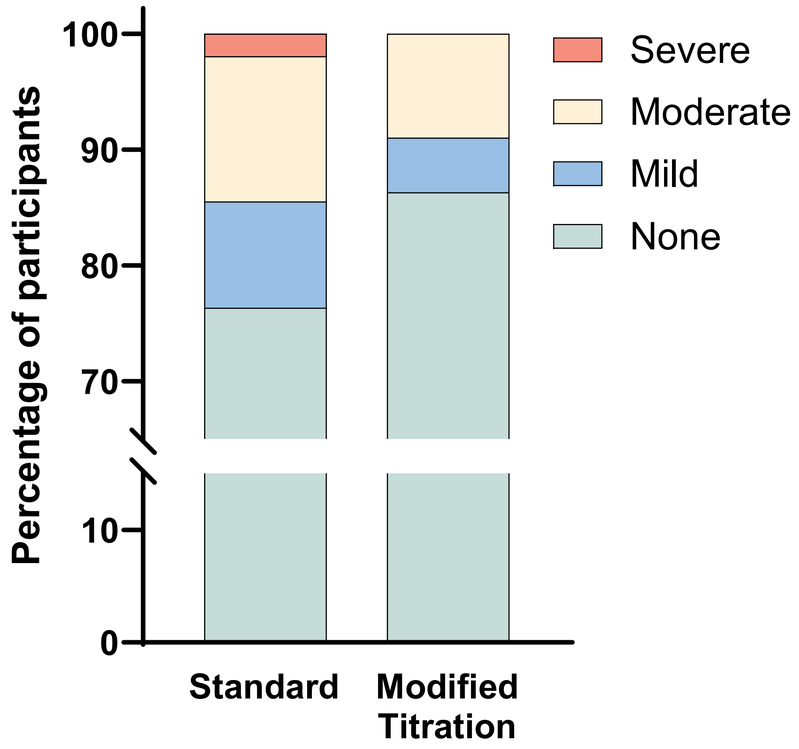
Significantly lower ARIA-E risk over time in the modified titration arm

Cumulative hazard of time to first ARIA-E



*Log-rank unstratified p-value (2-sided)

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



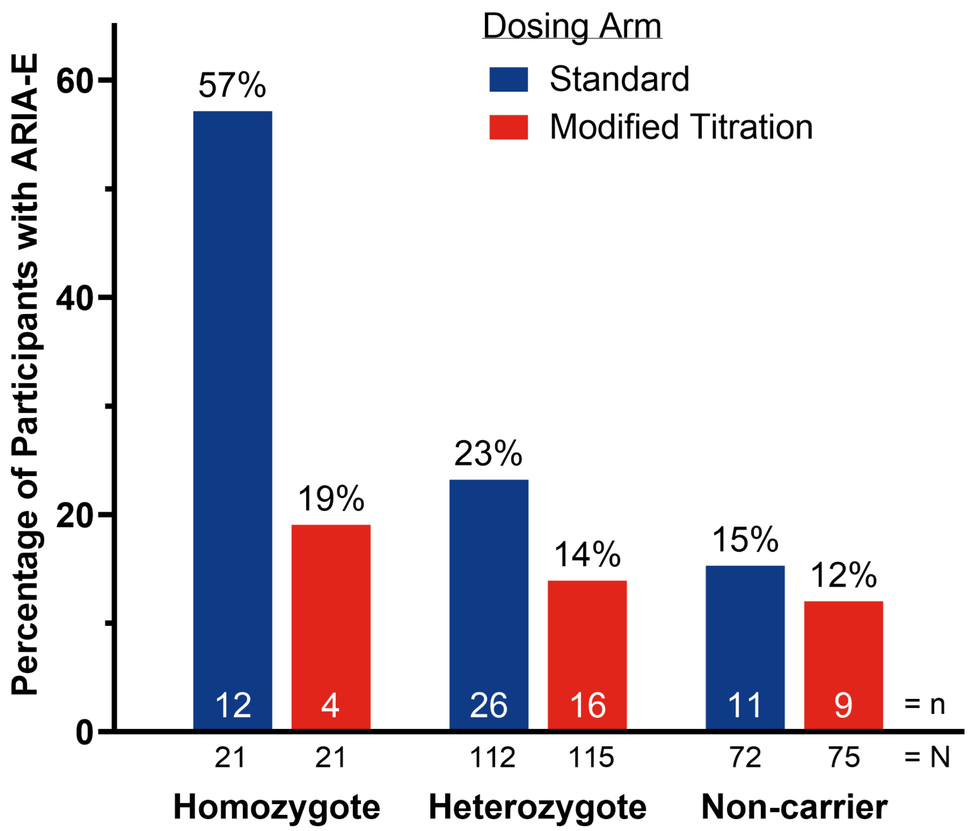
ARIA-E severity distribution is significantly shifted toward none or less severe direction in the modified titration arm with p=0.011 (Cochran-Mantel-Haenszel test)

86% of participants in the modified titration arm have no ARIA-E by MRI through Week 24

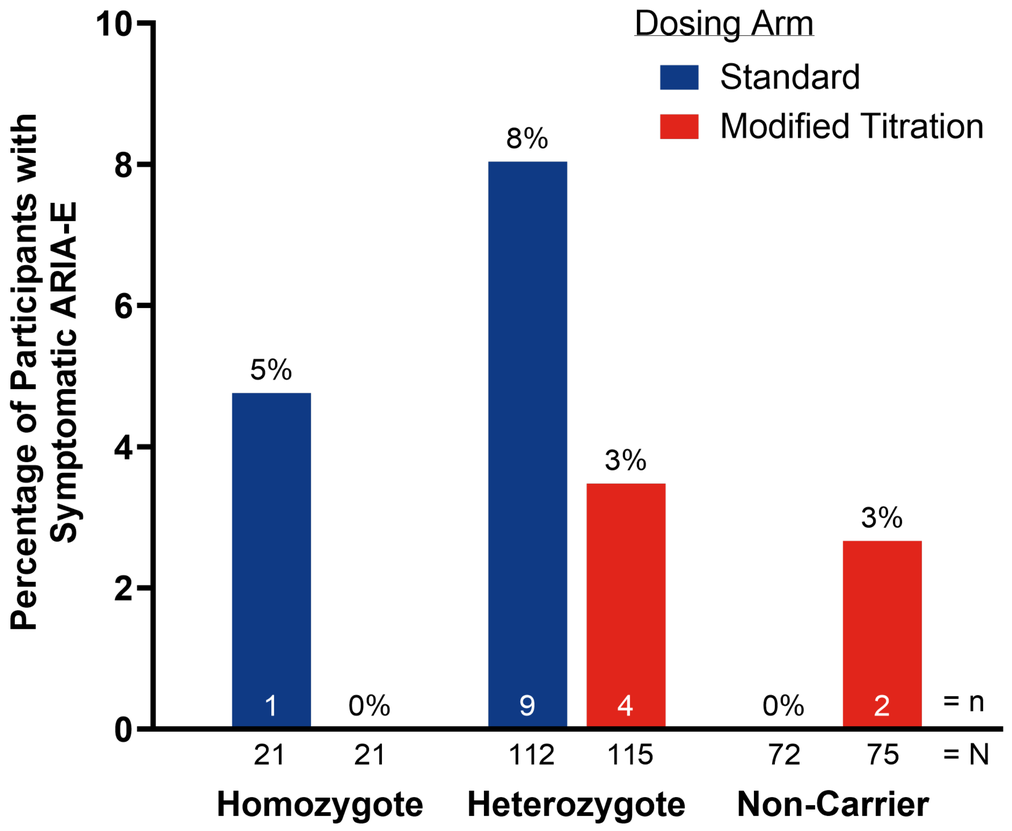
Abbreviations: ARIA-E=amyloid-related imaging abnormalities edema; MRI=magnetic resonance imaging

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

ARIA-E



Symptomatic ARIA-E



APOE: apolipoprotein E; N: number of participants in the analysis population; n: number of participants within each specific category

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.

ARIA: Amyloid-related imaging abnormalities; MRI: magnetic resonance imaging; N: number of participants in the analysis population; n: number of participants within each specific category; SAE: serious adverse event; SD: standard deviation; TEAE: treatment-emergent adverse event.

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 Adverse Event, n (%)	4 (1.9)	5 (2.4)
Discontinuations from Study Treatment due to an Adverse Event, n (%)	8 (3.9)	11 (5.2)
Treatment-Emergent Adverse Events, n (%)	175 (84.5)	181 (85.4)
Treatment-Emergent Adverse Events Related to Study Treatment [c], n (%)	104 (50.2)	103 (48.6)

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.

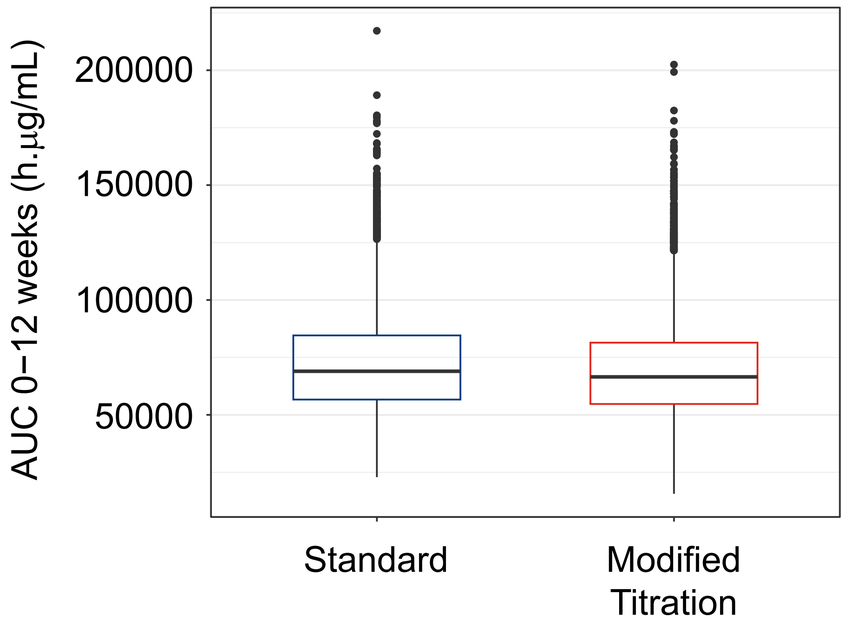
Treatment-emergent AEs ≥5% in standard dosing or modified titration arms

Category	Standard (N=207) n (%)	Modified Titration (N=212) n (%)
Participants with ≥1 TEAE	175 (84.5)	181 (85.4)
Amyloid related imaging abnormality-oedema/effusion	49 (23.7)	29 (13.7)
Headache	41 (19.8)	32 (15.1)
Amyloid related imaging abnormality-microhaemorrhages and haemosiderin 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)
Diarrhoea	12 (5.8)	6 (2.8)
Fatigue	11 (5.3)	12 (5.7)
Superficial siderosis of central nervous system	12 (5.8)	5 (2.4)
Arthralgia	8 (3.9)	13 (6.1)

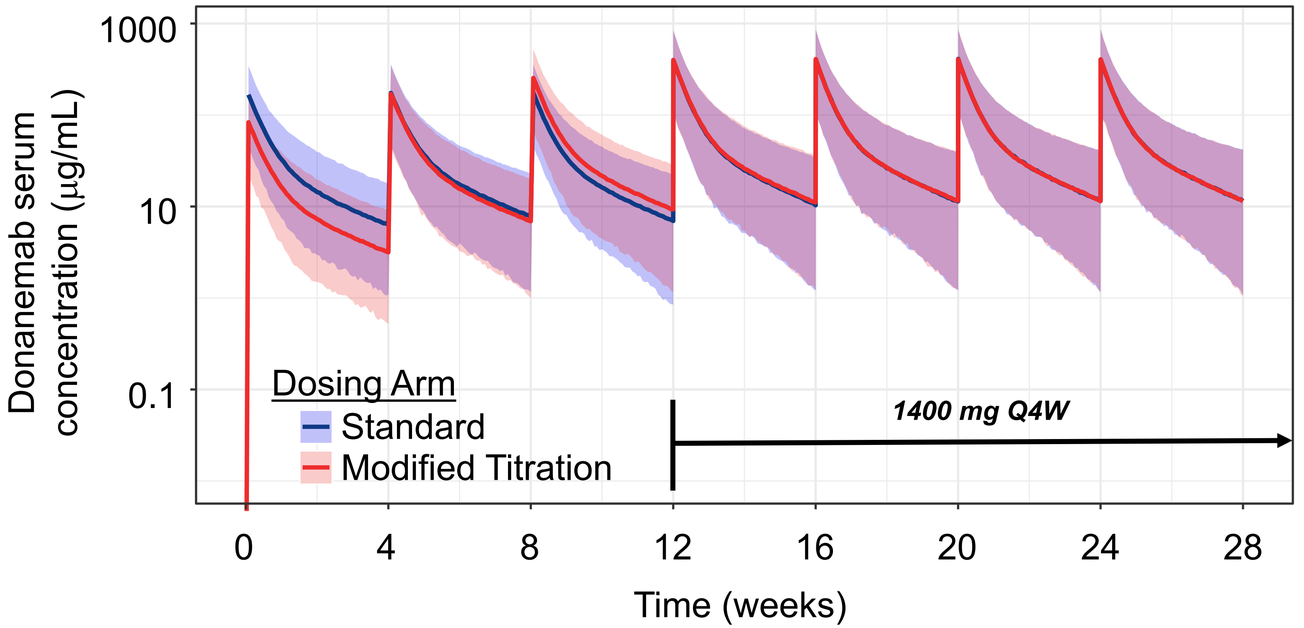
Note: MedDRA Version 27.0
AE: adverse event; N: number of participants in the analysis population; n: number of participants within each specific category; COVID-19: Coronavirus Disease 2019; TEAE: Treatment-emergent adverse event

Comparable cumulative exposure in the modified titration and standard dosing arms

Comparable cumulative exposure (0-12 weeks)



Concentration-time profiles over 24 weeks



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, number of participants: ~200 per arm): population pharmacokinetic method to estimate serum exposure

AUC: area under the curve; Q4W: every 4 weeks

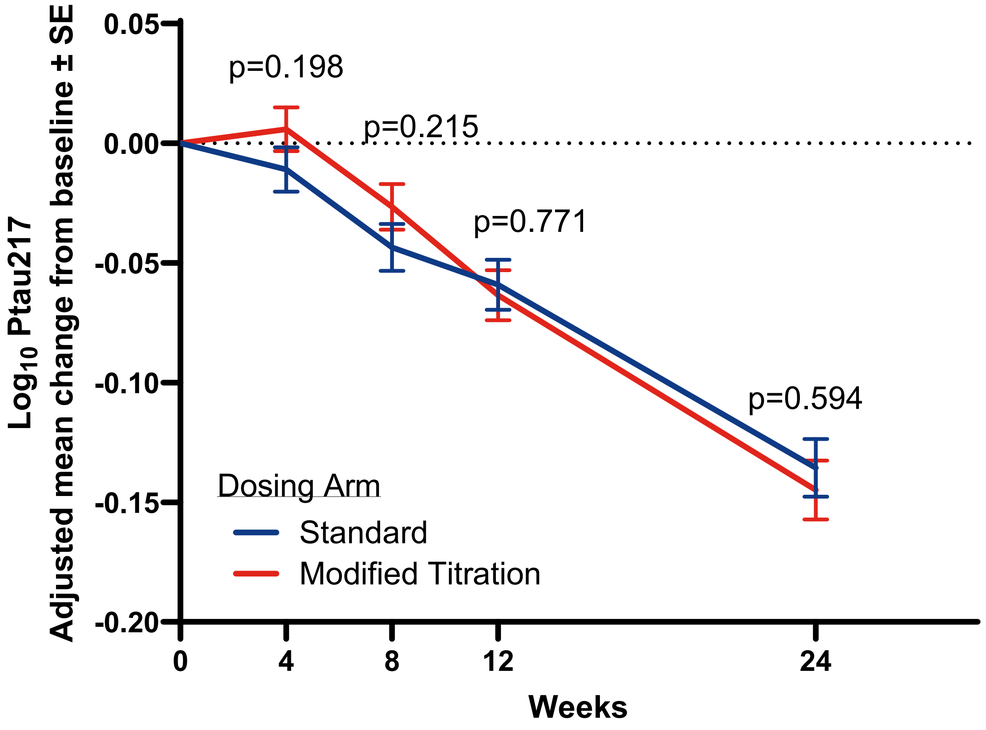
Comparable lowering of amyloid and P-tau217 over 24 weeks with standard dosing and modified titration

Comparable amyloid reduction

	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.
ANCOVA: analysis of covariance; CL: Centiloid; PET: positron emission tomography; SE: standard error; n: number of participants within each specific category

Comparable plasma P-tau217 reduction



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

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

Scan the QR code or use this URL
https://lillyscience.lilly.com/congress/ctad2024
for a list of all Lilly content presented at the congress