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ORIGINAL RESEARCH

Donanemab in Japanese Patients with Early Alzheimer's Disease: Subpopulation Analysis of the TRAILBLAZER-ALZ 2 Randomized Trial

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ABSTRACT

Introduction: Donanemab, a monoclonal antibody directed against an insoluble, modified, N-terminal truncated form of amyloid beta, demonstrated efficacy and safety in patients with early, symptomatic Alzheimer's disease (AD) in the phase 3 TRAILBLAZER-ALZ 2 trial. Here, we report clinical outcomes, biomarkers, and safety results for the Japanese subpopulation.

Methods: TRAILBLAZER-ALZ 2 (N = 1736) was conducted in eight countries, including Japan (enrollment June 2020–November 2021; database lock April 2023). Participants (60–85 years) with early, symptomatic AD (mild cognitive impairment/mild dementia), Mini-Mental State Examination score 20–28, and confirmed amyloid and tau pathology were randomized 1:1 (stratified by tau status) to intravenous donanemab (700 mg for three doses, then 1400 mg/dose) or placebo every 4 weeks for 72 weeks. Primary outcome was change from baseline to week 76 in integrated Alzheimer's Disease Rating Scale (iADRS) score. Other outcomes included clinical measures of cognitive and functional impairment, biomarkers, and safety.

Results: Of 88 Japanese participants (43 placebo, 45 donanemab), 7 in each group discontinued. Least-squares mean (LSM) change from baseline in iADRS score at week 76 was smaller with donanemab than with placebo in the combined (low-medium tau and high tau) and low-medium tau (N = 76) subpopulations (LSM change difference: 4.43 and 3.99, representing 38.8% and 40.2% slowing of disease progression, respectively). Slowing of AD progression with donanemab was also observed for other clinical outcomes. Marked decreases in amyloid plaque and plasma phosphorylated tau 217 were observed; amyloid clearance (< 24.1 Centiloids) was observed in 83.3% of the combined donanemab and 0% of the combined placebo groups. Amyloid-related imaging abnormalities of edema/effusions occurred in ten (22.2%) donanemab-treated participants (one [2.2%]

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symptomatic) and one (2.3%) placebo-treated participant.
Conclusions: The overall efficacy and safety of donanemab in Japanese participants were similar to the global TRAILBLAZER-ALZ 2 population.
Trial registration: ClinicalTrials.gov identifier: NCT04437511.

Keywords: Alzheimer disease; Amyloid plaque; Amyloid-related imaging abnormalities; Clinical Dementia Rating Scale; Donanemab; Integrated Alzheimer's Disease Rating Scale; Japan; Mild cognitive impairment/mild dementia; Positron-emission tomography; Tau proteins

INTRODUCTION

Alzheimer's disease (AD) is a progressive neurodegenerative disease that is usually first recognized clinically by the onset of cognitive impairment [1]. Although the molecular mechanisms underlying AD are complex, the formation of extracellular amyloid plaques in the cerebral cortex is considered an initiating event [2–5]. Intracellular neurofibrillary tangles containing the highly phosphorylated protein tau are also present, and there is evidence for synergies between tau and amyloid that contribute to the progression of AD [6]. Standard pharmacologic agents for AD, such as acetylcholinesterase inhibitors and memantine, are considered symptomatic treatment and do not target or affect the underlying pathology of the disease [1]. Recently, a number of amyloid-targeting monoclonal antibodies (mAbs) have been developed in the hope that these treatments may slow the progression of AD, especially if administered in the early stages [7, 8].

Donanemab is an immunoglobulin G1 mAb directed against an insoluble, modified, N-terminal truncated form of amyloid beta (N3pGlu Aβ) present only in brain amyloid plaques [9]. Donanemab binds to N3pGlu Aβ and aids plaque removal through microglial-mediated phagocytosis [9]. The potential efficacy of donanemab in the treatment of early, symptomatic AD was first demonstrated in the phase 2 TRAILBLAZER-ALZ trial [10]. Donanemab treatment resulted in a significantly smaller reduction in the integrated Alzheimer's Disease Rating Scale (iADRS) score, a composite score for cognition and activities of daily living [11], over 76 weeks compared with placebo [10]. These results were confirmed in the global, phase 3 TRAILBLAZER-ALZ 2 trial (least-squares mean [LSM] change from baseline in iADRS: − 10.19 for donanemab vs. − 13.11 for placebo, difference 2.92 [95% confidence interval, (CI), 1.51–4.33], $p < 0.001$ in the combined, i.e., overall] population) [12]. In addition to meeting the primary iADRS outcome, donanemab was associated with slowing of disease progression based on several clinical measures (Clinical Dementia Rating Scale-Sum of Boxes [CDR-SB], Alzheimer's Disease Assessment Scale-Cognitive Subscale (13-item) (ADAS-Cog_{13}), Alzheimer's Disease Cooperative Study-Activities of Daily Living Inventory, instrumental items [ADCS-iADL]) as well as by marked decreases in biomarkers, including amyloid plaque level and plasma phosphorylated tau 217 (P-tau217) [12]. These results were more pronounced in participants with low to medium levels of tau pathology based on positron emission tomography (PET) [12]. As reported for other amyloid-targeting antibodies [10, 13–15], the incidence of amyloid-related imaging abnormalities (ARIA) and infusion-related reactions was higher in the donanemab group than in the placebo group [12].

In Japan, the prevalence of AD and other dementias has been increasing rapidly over recent decades [16–19], and an analysis of 2019 Global Burden of Disease data reported that the rate of AD increase in the Japanese population is among the highest in the world [20]. Dementia currently affects > 5 million people in Japan, and an estimated 4 million have AD [20, 21]. The prevalence of dementia among Japanese people aged 65 years and older is expected to exceed 25% by 2035 [17]. With the rapid aging of the Japanese population, the number of people living with AD will increase markedly in the near future. Despite this, no published study to date has examined the efficacy of amyloid-targeting antibodies specifically in Japanese patients with AD, although Japanese

subpopulation results of phase 3 aducanumab trials have been published in abstract form [22]. In addition, the safety of amyloid-targeting antibodies in Japanese patients has only been reported as part of preliminary, single-dose, pharmacokinetic studies of discontinued compounds (solanezumab, bapineuzumab) [23, 24]. Here, we report key clinical outcomes, biomarkers, and safety results for the Japanese subpopulation of TRAILBLAZER-ALZ 2.

METHODS

Study design

TRAILBLAZER-ALZ 2 (ClinicalTrials.gov Identifier: NCT04437511) was a global, phase 3, randomized, placebo-controlled trial of donanemab conducted at 277 sites in eight countries [12], including 31 sites in Japan. Participants were enrolled between June 19, 2020, and November 5, 2021, with the database lock for the 76-week double-blind period occurring on April 28, 2023. The trial was conducted according to the Declaration of Helsinki, the International Council for Harmonisation Guideline for Good Clinical Practice, and local regulatory requirements. The protocol was approved by ethics review boards at each study site (Supplemental Table S1). Participants and their study partners provided written informed consent before any study procedures were conducted. An independent data safety monitoring board provided trial oversight.

Study population

Participants aged 60 to 85 years were eligible for inclusion if they had early, symptomatic AD characterized by gradual and progressive change in memory function, a Mini-Mental State Examination (MMSE) score of 20 to 28, and confirmed AD pathology based on PET for both amyloid (assessed with ^{18}F-florbetapir[13] or ^{18}F-florbetaben[14]) and tau (^{18}F-flortaucipir). Participants also had to have magnetic resonance imaging (MRI) with ≤ 4 cerebral microhemorrhages, ≤ 1 area of superficial siderosis, no amyloid-related imaging abnormalities of edema or effusions (ARIA-E), no intracerebral hemorrhage > 1 cm, and no severe white matter disease. Full eligibility criteria were described previously [12].

Treatment protocol

Randomization was performed using a computer-generated sequence and interactive web-response system, with stratification by tau pathology (low-medium tau or high tau) and study site. Baseline tau levels were categorized based on visual and quantitative PET scans [10, 12, 25–27]. Enrolled participants were randomized 1:1 to intravenous donanemab (700 mg for three doses, followed by 1400 mg per dose) or placebo every 4 weeks for 72 weeks, with final efficacy and safety data for the double-blind period collected at week 76. Participants in the donanemab group were switched to placebo in a blinded manner if their amyloid level was < 11 Centiloids at any single PET scan (week 24, week 52, or week 76) or was ≥ 11 but < 25 Centiloids at two consecutive PET scans.

Outcome measures

Details of the study outcomes have been described in the global TRAILBLAZER-ALZ 2 publication [12]. All outcomes reported herein were prespecified for the combined (low-medium tau + high tau) population and the low-medium tau population, including the Japanese subpopulation. The primary outcome was the change from baseline to week 76 in iADRS score. The iADRS is a validated scoring system that combines the ADAS-Cog$_{13}$ with the ADCS-iADL [11]. The iADRS has been used in previous clinical trials to measure the level of impairment in cognition and daily functioning in participants with early AD [10, 28, 29]. iADRS scores range from 0 to 144, with lower scores indicating greater deficit [29].

Other clinical outcomes reported for the Japanese subpopulation include changes from baseline to week 76 in the CDR-SB (range 0–18, higher scores indicate greater impairment),

ADAS-Cog_{13} (range 0–85, higher scores indicate greater overall cognition deficit), and ADCS-iADL (range 0–59, lower scores indicate greater impairment in daily function) as secondary outcomes, and slowing of disease progression based on iADRS and CDR-SB, the proportion of participants with no progression by CDR-SB at week 52, and the risk of progression to the next stage of disease based on the CDR–Global Score (CDR-GS; range 0 [no dementia] to 3 [severe dementia]) score as exploratory outcomes.

Biomarker outcomes reported for the Japanese subpopulation include the change from baseline to week 76 in amyloid plaque level (in Centiloids) and the proportion of participants achieving amyloid clearance (defined as < 24.1 Centiloids measured by PET) at weeks 24, 52, and 76 as secondary outcomes and the change from baseline to week 76 in P-tau217 [30] as an exploratory outcome. Plasma P-tau217 was measured using the plasma tau multianalyte assay (C_2N Diagnostics, St. Louis, MO, USA). Imaging (amyloid and tau PET) was performed locally and assessed centrally. Plasma biomarkers were measured at a central laboratory.

Safety was a secondary outcome and included the incidence of treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), deaths, adverse events (AEs) leading to study or treatment discontinuation, and TEAEs related to study treatment. AEs were classified using the Medical Dictionary for Regulatory Activities (MedDRA) version 25.1. AEs of special interest for amyloid-targeting antibodies [10, 13–15] included ARIA-E, ARIA of microhemorrhages and hemosiderin deposits (ARIA-H), and infusion-related reactions. ARIA and macrohemorrhage events were analyzed by MedDRA Preferred Term (PT) and also by central MRI analysis/TEAE PT cluster.

Statistical analysis

Sample size calculations for the global trial based on statistical power were described previously and were based on the low-medium tau population [12]; no power calculations were performed for the Japanese subpopulation. Analyses of clinical and biomarker outcomes were conducted on the efficacy evaluable set of the Japanese subpopulation, which consisted of all randomized participants with baseline and at least one post-baseline measurement. Outcomes were analyzed separately for the combined population and for the low-medium tau population. Outcomes in the high tau population, which were analyzed post hoc for the global trial [12], were not conducted for the Japanese subpopulation because of the small number of participants ($n = 5$ in the donanemab group, $n = 7$ in the placebo group).

Statistical analyses were as previously described, with imputation of missing data [12]. Imputation was used for the ADCS-iADL if $<$ 30% was missing, for the ADAS-Cog_{13} if ≤ 3 items were missing, and for CDR if one box was missing. If the number of missing items was larger than the number defined, the total score at that visit was considered missing. The iADRS score was considered missing if either the ADCS-iADL or ADAS-Cog_{13} score was missing. For clinical outcomes, changes from baseline in iADRS, ADAS-Cog_{13}, and ADCS-iADL were analyzed by a natural cubic spline model with two degrees of freedom (NCS2) as the primary analyses and by a mixed model for repeat measures (MMRM) as sensitivity analyses. Changes from baseline in CDR-SB score were analyzed by MMRM as the primary analysis and by NCS2 as a sensitivity analysis. Slowing of disease progression by iADRS and CDR-SB scores was expressed as a percentage by dividing the LSM change difference at week 76 (donanemab—placebo) by the LSM change from baseline at week 76 in the placebo group. Delay in disease progression was estimated using a time progression model for repeated measures [31]. The probability of no progression at week 52, defined as CDR-SB score change from baseline ≤ 0, was estimated using a generalized linear mixed model. The risk of progression across 76 weeks, in which progression was defined as any increase from baseline in CDR-GS at two consecutive visits, was estimated using a Cox proportional hazards model.

For biomarkers (amyloid and plasma P-tau217), changes from baseline were analyzed by an MMRM. For the proportion of participants with amyloid clearance, 95% CIs were

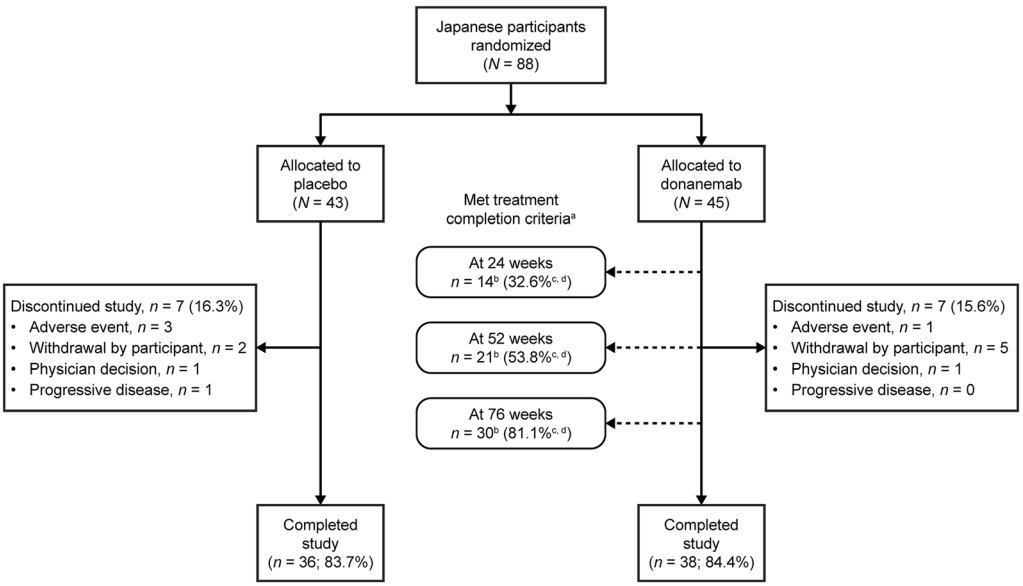

Fig. 1 Participant flow diagram. [a]Treatment completion criteria: if the amyloid plaque level was < 11 Centiloids on any one scan or ≥ 11 and < 25 Centiloids on two consecutive scans. [b]*n* = number of participants who met treatment completion criteria and had a PET scan at the visit. Note: Dashed lines indicate these participants were included in the discontinuation and completion boxes for the donanemab group. [c]Percentage calculated as n/number of participants with a PET scan at visit: *n* = 43 at 24 weeks, *n* = 39 at 52 weeks, and *n* = 37 at 76 weeks. [d]Corresponding number of participants and percentages for the low-medium tau population were *n* = 14 (36.8%) at 24 weeks, *n* = 19 (55.9%) at 52 weeks, and *n* = 28 (84.8%) at 76 weeks. *PET* positron emission tomography

calculated using the Wilson score method. Frontal lobe tau PET standardized uptake value ratio (SUVr) was analyzed by analysis of covariance.

Safety analyses were conducted on all Japanese randomized participants exposed to the study drug in the combined population.

Analyses were conducted using SAS version 9.4 (SAS Institute) or R Project version 4.3.0 (R Foundation).

RESULTS

Participant disposition and baseline characteristics

Of 1736 participants randomized globally [12], 88 (5.1%) were from Japan; of these, 43 were allocated to placebo and 45 to donanemab (Fig. 1). Seven participants (16.3%) in the placebo group discontinued the study, with *n* = 3, because of an AE; seven participants in the donanemab group (15.6%) discontinued, with *n* = 5 because of withdrawal by the participant. A total of 74 (84.1%) participants completed the 76-week double-blind period.

Within the Japanese subpopulation, baseline participant characteristics were similar in the donanemab and placebo treatment groups, except for the proportion of female participants and the proportion of participants who were apolipoprotein E ε4 carriers being somewhat higher in the donanemab group than in the placebo group (Table 1). Baseline characteristics were also generally similar to those in the global trial population, although the proportion of participants with low-medium tau was higher (86.4% for Japan vs. 68.1% for global) [12].

Table 1 Baseline demographics, clinical measures, and biomarker measures in the Japanese subpopulation of TRAILBLAZER-ALZ 2

Variable	Combined population		Low-medium tau population	
	Placebo (*N* = 43)	Donanemab (*N* = 45)	Placebo (*N* = 36)	Donanemab (*N* = 40)
Sex, *n* (%) female	23 (53.5)	33 (73.3)	20 (55.6)	30 (75.0)
Age, mean (SD), years	73.95 (5.95)	73.04 (5.90)	75.11 (5.42)	73.85 (5.45)
Education of $\geq$ 13 years, *n* (%)	21 (48.8)	20 (44.4)	17 (47.2)	17 (42.5)
APOE ε4 carrier, *n* (%)	23 (53.5)	31 (68.9)	19 (52.8)	28 (70.0)
AChEi and/or memantine use, *n* (%)	24 (55.8)	29 (64.4)	18 (50.0)	25 (62.5)
Clinical measures,[a] mean (SD)				
iADRS score	100.72 (12.76)	103.27 (10.71)[b]	102.36 (12.90)	102.69 (10.80)
ADAS-Cog_{13} score	29.98 (7.43)	29.62 (6.19)	29.03 (7.40)	29.70 (6.14)
ADCS-iADL score	45.70 (7.85)	47.95 (6.69)[b]	46.39 (7.30)	47.46 (6.85)
ADCS-ADL score	64.60 (7.93)	66.70 (7.01)[b]	65.36 (7.29)	66.18 (7.19)
MMSE score[c]	22.60 (3.01)	22.87 (2.79)	22.92 (3.04)	22.90 (2.85)
CDR-SB score	3.79 (2.20)	3.58 (1.68)[b]	3.51 (2.18)	3.58 (1.70)
CDR-GS,[a] *n* (%)				
0	1 (2.3)	0 (0.0)	1 (2.8)	0 (0.0)
0.5	31 (72.1)	33 (75.0)	28 (77.8)	30 (76.9)
1	9 (20.9)	10 (22.7)	5 (13.9)	8 (20.5)
2	2 (4.7)	1 (2.3)	2 (5.6)	1 (2.6)
Missing	0	1	0	1
Biomarker measures, mean (SD)				
Amyloid PET, Centiloids[d]	87.34 (31.34)	81.28 (30.62)	89.89 (33.30)	80.76 (29.56)
Tau PET AD signature-weighted SUVr[d,e]	1.27 (0.20)	1.24 (0.18)	1.20 (0.13)	1.20 (0.12)

Table 1 continued

Variable	Combined population		Low-medium tau population	
	Placebo (N = 43)	Donanemab (N = 45)	Placebo (N = 36)	Donanemab (N = 40)
Plasma P-tau217, log_{10}	0.70 (0.18)	0.72 (0.22)	0.67 (0.16)	0.71 (0.21)

AChEi acetylcholinesterase inhibitor(s), *AD* Alzheimer's disease, *ADAS-Cog$_{13}$* Alzheimer's Disease Assessment Scale-Cognitive Subscale (13-item), *ADCS-ADL* Alzheimer's Disease Cooperative Study-Activities of Daily Living Inventory, *ADCS-iADL* Alzheimer's Disease Cooperative Study–Activities of Daily Living Inventory, instrumental items, *APOE* apolipoprotein E, *CDR-GS* Clinical Dementia Rating–Global Score, *CDR-SB* Clinical Dementia Rating Scale-Sum of Boxes, *iADRS* integrated Alzheimer's Disease Rating Scale, *MMSE* Mini-Mental State Examination, *PERSI* parametric estimation of reference signal intensity, *PET* positron emission tomography, *P-tau217* phosphorylated tau 217, *SD* standard deviation, *SUVr* standardized uptake value ratio

Numbers of participants with nonmissing data were used as denominators to calculate percentages

[a]Clinical measure ranges: iADRS scores 0–144 (lower scores indicate greater impairment); ADAS-Cog$_{13}$ scores 0–85 (higher scores indicate greater overall cognition deficit); ADCS-iADL scores 0–59 (lower scores indicate greater impairment in daily function); ADCS-ADL scores 0–78 (lower scores indicate greater impairment); MMSE scores 0–30 (lower scores indicate greater impairment); CDR-SB scores 0–18 (higher scores indicate greater impairment); CDR-GS scores 0 (no dementia) to 3 (severe dementia)

[b]N = 44

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

[d]Based on screening data

[e]SUVr with respect to a reference signal intensity in white matter parametric estimation of reference signal intensity (PERSI)

Primary outcome: iADRS change from baseline

The LSM change from baseline in iADRS score at week 76 was smaller in the donanemab group than in the placebo group (Fig. 2; Table 2). In the combined population, the LSM (95% CI) change difference between donanemab and placebo by NCS2 analysis was 4.43 (− 0.17, 9.03), representing a 38.8% slowing of clinical progression. In the low-medium tau population, the LSM (95% CI) change difference between donanemab and placebo by NCS2 analysis was 3.99 (− 0.98, 8.97), representing a 40.2% slowing of clinical progression. Similar results were seen when analyzed by an MMRM (Table 2).

Other clinical outcomes

CDR-SB and CDR-GS

For the CDR-SB score change from baseline to week 76, the LSM (95% CI) change difference between donanemab and placebo (as analyzed by an MMRM) in the combined population was − 0.23 (− 1.33, 0.87), with a 14.2% slowing of progression in the combined population and 0.08 (− 1.03, 1.20), with a − 7.4% slowing of progression in the low-medium tau population (Table 2). It was noted that two participants in the placebo group of the low-medium tau population had large improvements from baseline in CDR-SB score; when analyses were repeated with these participants excluded, the difference between placebo and donanemab at weeks 52 and 76 was increased (Supplemental Fig. S1). The probability of no progression at week 52 by CDR-SB score was 0.47 for donanemab and 0.25 for placebo in the combined population and 0.51 for donanemab and 0.33 for placebo in the low-medium tau population. Based on CDR-GS, the risk of disease progression to the next AD stage over 76 weeks was 33.9% lower [hazard ratio (HR) 0.661 (95% CI 0.256, 1.703)] in the combined population and 25.7% lower [HR 0.743 (95% CI 0.258, 2.143)] in the low-

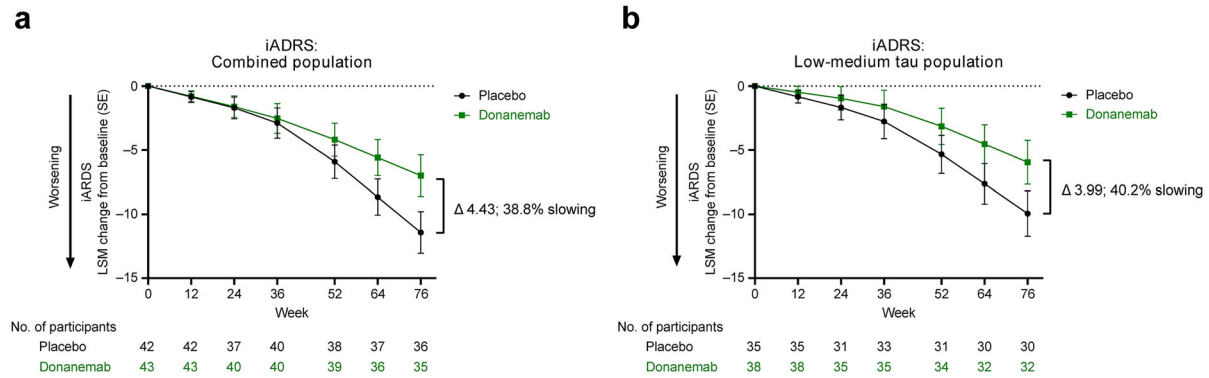

Fig. 2 LSM (SE) change from baseline in iADRS with placebo or donanemab treatment in **a** the combined population and **b** the low-medium tau population. The analysis used a natural cubic spline model with two degrees of freedom adjusted for basis expansion terms (two terms), basis expansion term-by-treatment interaction, and covariates for age at baseline, pooled investigator, baseline tau level (combined population only), and baseline acetylcholinesterase inhibitor/memantine use. *iARDS* integrated Alzheimer's Disease Rating Scale, *LSM* least-squares mean, *SE* standard error

medium tau population with donanemab compared with placebo (Table 2).

ADAS-Cog$_{13}$ and ADCS-iADL

For the ADAS-Cog$_{13}$ score change from baseline to week 76 by NCS2, the LSM (95% CI) change difference between donanemab and placebo was − 2.71 (− 4.97, − 0.46), with a 50.3% slowing of progression in the combined population and − 1.52 (− 3.72, 0.67), with a 39.0% slowing of progression in the low-medium tau population (Table 2). For the ADCS-iADL score change from baseline to week 76 by NCS2, the LSM (95% CI) change difference between donanemab and placebo was 1.24 (− 2.44, 4.91), with a 26.9% slowing of progression in the combined population, and 1.54 (− 2.55, 5.63), with a 33.1% slowing of progression in the low-medium tau population.

Biomarkers

The LSM change from baseline in amyloid plaque level measured by PET was greater in the donanemab group than in the placebo group at 24, 52, and 76 weeks in both the combined and low-medium tau Japanese populations (Fig. 3; Table 3). In the donanemab group, amyloid decreased by an LSM of 72.27 Centiloids in the combined population and by an LSM of 74.91 Centiloids in the low-medium tau population at week 76 (Fig. 3). In contrast, small increases in amyloid were observed in the placebo group. Amyloid clearance (defined as < 24.1 Centiloids) in the donanemab group was achieved in the combined and low-medium tau populations, respectively, by 46.5% and 50.0% of participants at week 24, 71.8% and 76.5% at week 52, and 83.3% and 87.5% at week 76 (Fig. 4; Table 3). These proportions were greater than in the placebo group where no participants achieved amyloid clearance at any time point. Of participants in the donanemab group who had a PET scan at the week 24, week 52, or week 76 visits, 32.6%, 53.8%, and 81.1%, respectively, met the treatment completion criteria based on amyloid plaque level (Fig. 1).

Greater decreases in plasma P-tau217 were seen in the donanemab-treated group compared with placebo at weeks 12, 24, 52, and 76 for both the combined and low-medium tau populations (Fig. 5; Table 3).

There was no difference between donanemab and placebo in frontal lobe tau SUVr change from baseline in either the combined or the low-medium tau Japanese population (Table 3).

Table 2 Clinical outcomes in the Japanese combined and low-medium tau populations

Outcome	Combined population		Low-medium tau population	
	LSM change difference between donanemab and placebo (95% CI) (unless otherwise described)	**% Slowing[a]**	**LSM change difference between donanemab and placebo (95% CI) (unless otherwise described)**	**% Slowing[a]**
iADRS				
Change from baseline to Week 76				
NCS2 (primary analysis)[b]	4.43 (− 0.17, 9.03)	38.8	3.99 (− 0.98, 8.97)	40.2
MMRM (sensitivity analysis)[c]	3.25 (− 1.51, 8.01)	41.0	3.13 (− 1.87, 8.13)	39.3
Delay in disease progression at Week 76[c]	Delayed by 3.37 (95% CI 1.09, 5.66) months	NA	Delayed by 3.00 (95% CI − 3.49, 9.5) months	
CDR-SB				
Change from baseline to Week 76				
MMRM (primary analysis)[c]	− 0.23 (− 1.33, 0.87)	14.2	0.08 (− 1.03, 1.20)	− 7.4
NCS2 (sensitivity analysis)[b]	− 0.50 (− 1.55, 0.54)	27.1	− 0.04 (− 1.02, 0.94)	3.2
Delay in disease progression at Week 76[d]	Delayed by 0.82 (95% CI − 0.87, 2.51) months	NA	Delayed by 0.19 (95% CI − 2.37, 2.75) months	NA
No progression at Week 52[e]	Probability of no progression: 0.47 (vs. 0.25 for placebo)	NA	Probability of no progression: 0.51 (vs. 0.33 for placebo)	NA
CDR-GS				
Risk of progression[f]	HR (95% CI): 0.661 (0.256, 1.703)	NA	HR (95% CI): 0.743 (0.258, 2.143)	NA
ADAS-Cog_{13}				
Change from baseline to Week 76 (NCS2)[b]	− 2.71 (− 4.97, − 0.46)	50.3	− 1.52 (− 3.72, 0.67)	39.0

Table 2 continued

Outcome	Combined population		Low-medium tau population	
	LSM change difference between donanemab and placebo (95% CI) (unless otherwise described)	% Slowing[a]	LSM change difference between donanemab and placebo (95% CI) (unless otherwise described)	% Slowing[a]
ADCS-iADL				
Change from baseline to Week 76 (NCS2)[b]	1.24 (− 2.44, 4.91)	26.9	1.54 (− 2.55, 5.63)	33.1

AChEi acetylcholinesterase inhibitor(s), *ADAS-Cog$_{13}$* Alzheimer's Disease Assessment Scale-Cognitive Subscale (13-item), *ADCS-iADL* Alzheimer's Disease Cooperative Study–Activities of Daily Living Inventory, instrumental items, *CDR-GS* Clinical Dementia Rating-Global Score, *CDR-SB* Clinical Dementia Rating Scale-Sum of Boxes, *CI* confidence interval, *HR* hazard ratio, *iADRS* integrated Alzheimer's Disease Rating Scale, *LSM* least-squares mean, *MMRM* mixed model for repeat measures, *NA* not applicable, *NCS2* natural cubic spline model with two degrees of freedom

[a]Slowing of disease progression was expressed as a percentage by dividing the LSM change difference at week 76 (donanemab – placebo) by the LSM change from baseline at week 76 in the placebo group

[b]Changes from baseline in iADRS, CDR-SB, ADAS-Cog$_{13}$, and ADCS-iADL were analyzed by NCS2 adjusted for basis expansion terms (two terms), basis expansion term-by-treatment interaction, and covariates for age at baseline, pooled investigator, baseline tau category (combined population only), and baseline AChEi/memantine use

[c]Changes from baseline in iADRS and CDR-SB were also analyzed by MMRM with fixed factors for treatment, visit, treatment-by-visit interaction, and covariates for baseline score, baseline score-by-visit interaction, age at baseline, baseline tau category (combined population only), pooled investigator, and baseline AChEi/memantine use

[d]Delay in disease progression was estimated using a time-progression model for repeated measures adjusted for the fixed effects of baseline age, baseline AChEi/memantine use, baseline tau category (combined population only), and pooled investigator as covariates. The model assumed proportional time slowing, except for iADRS in the low-medium tau population in the global TRAILBLAZER-ALZ 2 population, which did not meet proportionality assumptions (based on a $p < 0.05$ in a likelihood ratio test); in this case, a nonproportionality assumption was used

[e]Probability of no progression at week 52, defined as CDR-SB score change from baseline ≤ 0, was estimated using a generalized linear mixed model with fixed factors for treatment, visit, treatment-by-visit interaction, and covariates for baseline score, baseline score-by-visit interaction, age at baseline, and baseline AChEi/memantine use

[f]Risk of progression across 76 weeks, in which progression was defined as any increase from baseline in CDR-GS at two consecutive visits, was estimated using a Cox proportional hazards model with covariates baseline age, baseline value, baseline tau category (combined population only), and baseline AChEi/memantine use, and stratified by pooled investigator

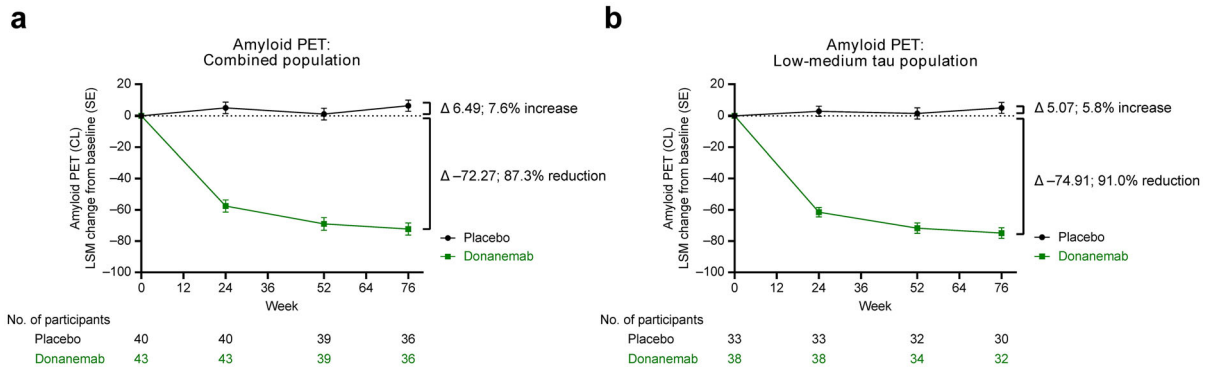

Fig. 3 LSM (SE) change from baseline in amyloid plaque level in Centiloids (by PET) with placebo or donanemab treatment in **a** the combined population and **b** the low-medium tau population. LSM clearance change from baseline and SE are derived using a mixed-model repeated-measures methodology with fixed factors for treatment, visit, treatment-by-visit interaction, and covariates for baseline score, baseline score-by-visit interaction, baseline tau category (combined population only), and age at baseline. *CL* Centiloid, *LSM* least-squares mean, *PET* positron emission tomography, *SE* standard error

Safety

In the combined population, SAEs occurred in eight (18.6%) Japanese participants in the placebo group and seven (15.6%) participants in the donanemab group (Table 4). There were no deaths in either treatment group. In the placebo group, three (7.0%) participants discontinued treatment because of an AE. In the donanemab group, four (8.9%) participants discontinued treatment because of an AE; of these, two (4.4%) were due to ARIA-E events and two (4.4%) were due to infusion-related reactions.

TEAEs were experienced by 33 (76.7%) participants in the placebo group and 41 (91.1%) participants in the donanemab group (Table 4). Of these, 9 (20.9%) and 22 (48.9%) had TEAEs deemed related to study treatment for placebo and donanemab, respectively. By PT, ARIA-H and ARIA-E were the most common TEAEs in the donanemab group (26.7% and 22.2%, respectively) and were observed at a lower incidence in the placebo group (7.0% and 2.3%, respectively). Other common (≥ 5% incidence) TEAEs in the donanemab group were COVID-19 (13.3%), arthralgia (11.1%), infusion-related reaction, back pain, and nasopharyngitis (6.7% each); these TEAEs occurred at a lower rate in the placebo group. TEAEs in the System Organ Class "musculoskeletal and connective tissue disorders" (including arthralgia) were also more common in the donanemab group than in the placebo group (31.1% vs. 9.3%).

When assessed by central MRI or TEAE cluster, 10 (22.2%) participants in the donanemab group had ARIA-E, 1 (2.2%) of which was symptomatic (confusional state), and 16 (35.6%) had ARIA-H (Table 5). In the placebo group, one (2.3%) and five (11.6%) participants had ARIA-E and ARIA-H, respectively. There were no intracerebral hemorrhages > 1 cm or SAEs of ARIA in either treatment group.

DISCUSSION

Given the rapidly increasing number of people in Japan who are living with AD [20, 21], advances in effective treatment options are urgently needed. In this analysis of the TRAILBLAZER-ALZ 2 Japanese subpopulation, the changes in clinical and biomarker outcomes with donanemab, as well as the safety profile of donanemab observed, were similar to those seen in the overall study population [12]. The results of TRAILBLAZER-ALZ 2 suggest that donanemab can help patients stay in early, symptomatic AD longer, a period when they have less cognitive and functional difficulty in their daily lives. This is important not only by extending the time that patients can continue

Table 3 Biomarker outcomes in the Japanese combined and low-medium tau populations

Biomarker	LSM change difference between donanemab and placebo (95% CI) (unless otherwise described)	
	Combined population	**Low-medium tau population**
Amyloid plaque change from baseline, Centiloids		
Week 24	− 62.69 (− 71.40, − 53.98)	− 64.40 (− 73.44, − 55.35)
Week 52	− 70.07 (− 79.38, − 60.77)	− 73.22 (− 83.13, − 63.31)
Week 76	− 78.76 (− 87.54, − 69.98)	− 79.98 (− 89.76, − 70.20)
Proportion with amyloid clearance (< 24.1 Centiloids), %		
Week 24	46.5 vs. 0.0 for placebo	50.0 vs. 0.0 for placebo
Week 52	71.8 vs. 0.0 for placebo	76.5 vs. 0.0 for placebo
Week 76	83.3 vs. 0.0 for placebo	87.5 vs. 0.0 for placebo
Plasma P-tau217 (log_{10}) change from baseline		
Week 24	− 0.28 (− 0.35, − 0.20)	− 0.28 (− 0.36, − 0.20)
Week 52	− 0.27 (− 0.34, − 0.21)	− 0.28 (− 0.34, − 0.21)
Week 76	− 0.31 (− 0.39, − 0.24)	− 0.32 (− 0.40, − 0.23)
Frontal lobe tau SUVr change from baseline[a]		
Week 76	0.0178 (− 0.293, 0.0649)	− 0.0027 (− 0.0489, 0.0435)

ANCOVA analysis of covariance, *CI* confidence interval, *LSM* least-squares mean, *MMRM* mixed model for repeat measures, *P-tau217* phosphorylated tau 217, *SUVr* standardized uptake value ratio

Unless otherwise indicated, LSM change from baseline and 95% CI derived using MMRM methodology with fixed factors for treatment, visit, treatment-by-visit interaction, and covariates for baseline score, baseline score-by-visit interaction, and age at baseline

[a]Referenced to cerebellar crus; LSM change from baseline and 95% CIs were derived using an ANCOVA model for endpoint measures with fixed factors for treatment, and covariates for baseline score and age, and, for the combined population only, also baseline tau category

to live independently but also by providing a preparatory period in which patients can continue their familiar lifestyle and familiar relationships in the community [32] as well as contributing to the development of a "living with dementia" society [33].

For the primary outcome, change from baseline to week 76 in iADRS score, the change difference between donanemab and placebo was slightly higher in Japanese participants compared with the global TRAILBLAZER-ALZ 2 population in both the combined (4.43 vs. 2.92) and low-medium tau (3.99 vs. 3.25) populations. These differences were also reflected in the slowing of clinical progression (38.8% and 22.3% in the combined population, and 40.2% and 35.1% in the low-medium tau population, for Japanese and global participants, respectively). Most other clinical outcomes were also similar between Japanese and global populations, with the exception of slowing of progression by CDR-SB. When analyzed by an MMRM, no slowing was observed in the Japanese low-medium tau population (− 7% slowing) in contrast to the global low-medium tau population (36% slowing) [12]. However, the sensitivity analysis by NCS2 (Table 2) resulted in slowing of progression rates in the Japanese subpopulation similar to those in the global analysis. On inspection, two participants in the

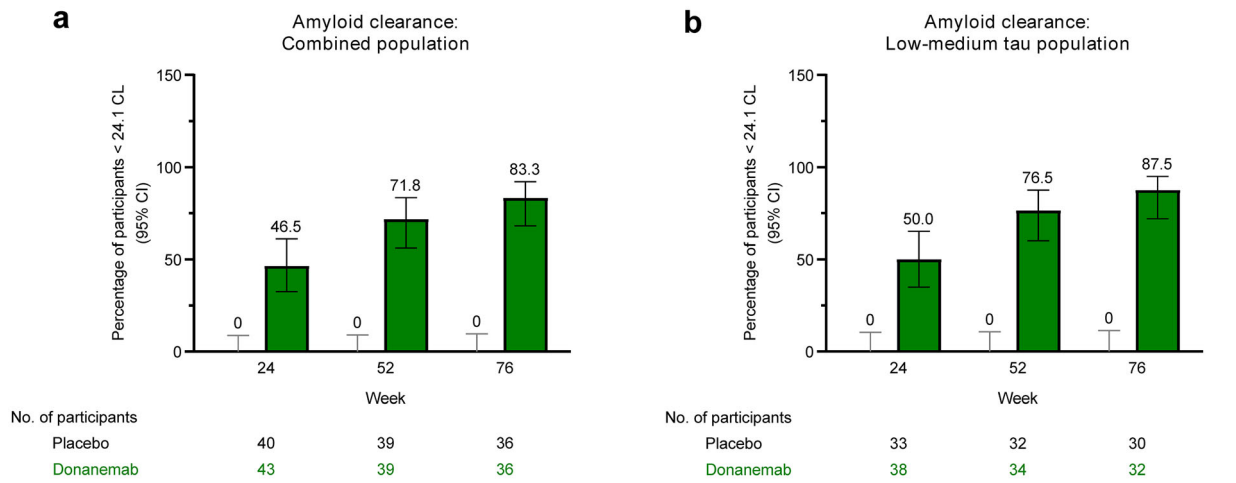

Fig. 4 Proportion (95% CI) of participants achieving amyloid clearance, defined as < 24.1 Centiloids, with placebo or donanemab treatment in **a** the combined population and **b** the low-medium tau population. CIs are calculated using the Wilson score method. *CI* confidence interval, *CL* Centiloid

placebo group were found to have disproportionately high baseline CDR-SB scores, resulting in large improvements from baseline to week 76; a reanalysis by the MMRM with these two participants removed resulted in a positive slowing of clinical progression by donanemab (Supplemental Fig. S1). A few such "outliers" with unusually large improvements in CDR-SB were also observed in the global population in both donanemab and placebo groups; it is likely that the two outliers in the Japanese subpopulation were both in the placebo group by chance because of the small sample size.

The identification of biomarkers for AD, particularly PET-based imaging of neuropathology, has greatly enhanced diagnosis and the monitoring of disease progression [1, 3, 34–36]. Donanemab treatment markedly reduced the level of amyloid by approximately 72–75 Centiloids in the Japanese subpopulation and by 87–88 Centiloids in the global population. Moreover, a majority participants in both populations achieved amyloid clearance (< 24.1 Centiloids) at each time point, with 83.3–87.5% of the Japanese donanemab group and 76.4–80.1% of the global donanemab group achieving clearance at week 76. The numerical differences between the global and Japanese populations in the absolute reduction of amyloid and the proportion achieving clearance may be related to differences in baseline amyloid levels (80.76–89.89 Centiloids vs. 100.9–103.5 Centiloids in the Japanese and global populations, respectively). Nevertheless, the amyloid results are consistent with the mechanism of action of donanemab, an antibody directed toward the amyloid protein present in plaques without interacting with other amyloid species [9]. Donanemab also dramatically reduced levels of the plasma biomarkers P-tau217, as seen in the global population [12]. Similar results were seen in the phase 2 TRAILBLAZER-ALZ trial of donanemab [37] as well as in a global phase 3 trial of another amyloid-targeting antibody, lecanemab [38].

The safety profile of donanemab in Japanese participants was similar to that seen in the global population, including a higher incidence of ARIA compared with placebo (40.0% vs. 14.0% in the Japanese subpopulation, 36.8% vs. 14.9% in the global population). As noted, ARIA events have been observed previously in phase 3 trials of aducanumab [39], lecanemab [38], and donanemab (TRAILBLAZER-ALZ 2) [12], as well

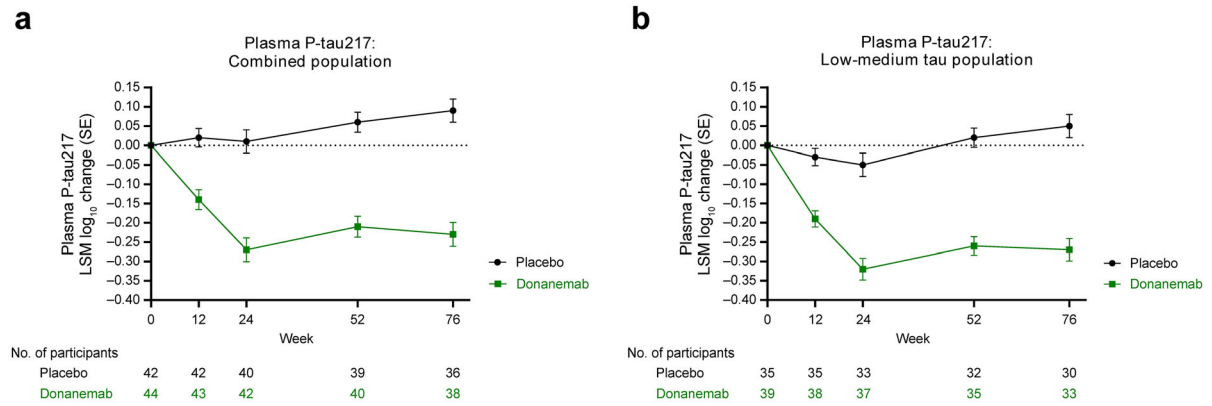

Fig. 5 LSM (SE) $\log_{10}$ change from baseline in plasma P-tau217 with placebo or donanemab treatment in **a** the combined population and **b** the low-medium tau population. LSM change from baseline and SE are derived using a mixed-model repeated-measures methodology with fixed factors for treatment, visit, treatment-by-visit interaction, baseline tau category (combined population only), and covariates for baseline score, baseline score-by-visit interaction, and age at baseline. *LSM* least-squares mean, *P-tau217* phosphorylated tau 217, *SE* standard error

as in trials of the earlier amyloid-targeting antibodies gantenerumab [40] and bapineuzumab [41]. Most cases of ARIA are asymptomatic and resolve with study drug discontinuation or dose reduction. In the global TRAILBLAZER-ALZ 2 trial, study drug discontinuations due to ARIA and SAEs of ARIA occurred at rates of 3.3% and 2.0%, respectively, while symptomatic ARIA-E occurred in 6.1% of donanemab-treated participants [12]. In the Japanese subpopulation, two participants (4.4%) discontinued treatment because of an ARIA event (both ARIA-E), there were no ARIA SAEs, and one participant (2.2%) with ARIA-E was symptomatic (confusional state). Although the sample size of the Japanese subpopulation was too small to directly compare the rates of these less-common events against the global population, our results suggest that Japanese patients are not more susceptible to ARIA than non-Japanese patients. We also observed a higher incidence of musculoskeletal and connective tissues TEAEs in the Japanese donanemab group than in the placebo group; this difference was not observed in the global population and may be related to the smaller sample size of the Japanese subpopulation.

This is the first analysis of an amyloid-targeting antibody in Japanese patients with AD participating in a large, randomized, placebo-controlled trial. The TRAILBLAZER-ALZ 2 trial assessed a broad range of clinical and biomarker outcomes, as well as safety, over 76 weeks and was designed with a blinded switch from donanemab to placebo in participants who achieved amyloid clearance [12]. To capture individuals in the early stages of AD, patients with MMSE scores from 20 to 28 were eligible for inclusion, meaning that some participants may have had only mild cognitive impairment at baseline (15.9% of the Japanese subpopulation had MMSE $\geq$ 27); these patients may have responded especially well to donanemab. The analyses were adjusted for a range of prespecified demographic and clinical characteristics; however, analyses were not adjusted for other potential confounding factors, such as APOE ε4 carrier status (which differed slightly between treatment groups). Although the sample size of the Japanese subpopulation was not powered to detect statistical differences, the safety and efficacy of donanemab were consistent with that of the global population [12]. In addition, the discontinuation rate was lower in the Japanese subpopulation than in the overall global

Table 4 Summary of adverse events in the Japanese combined population

Event, *n* (%)	**Placebo (*N* = 43)**	**Donanemab (*N* = 45)**
Overview of AEs[a]		
Death[b]	0 (0)	0 (0)
SAE	8 (18.6)	7 (15.6)
Study discontinuations due to AEs	3 (7.0)	1 (2.2)
Treatment discontinuations due to AEs	3 (7.0)	4 (8.9)
ARIA-E	1 (2.3)	2 (4.4)
Infusion-related reaction	0 (0)	2 (4.4)
TEAEs[c]	33 (76.7)	41 (91.1)
TEAEs deemed related to study treatment[d]	9 (20.9)	22 (48.9)
TEAEs ≥ 5% incidence in donanemab group by SOC and PT[e]		
Nervous system disorders	9 (20.9)	22 (48.9)
ARIA-H	3 (7.0)	12 (26.7)
ARIA-E	1 (2.3)	10 (22.2)
Infections and infestations	12 (27.9)	12 (26.7)
COVID-19	2 (4.7)	6 (13.3)
Nasopharyngitis	1 (2.3)	3 (6.7)
Injury, poisoning and procedural complications	11 (25.6)	11 (24.4)
Infusion-related reaction	0 (0)	3 (6.7)
Musculoskeletal and connective tissue disorders	4 (9.3)	14 (31.1)
Arthralgia	0 (0)	5 (11.1)
Back pain	1 (2.3)	3 (6.7)
Overview of ARIA[f]		
Any ARIA (-E or -H)	6 (14.0)	18 (40.0)
Any SAE of ARIA	0 (0)	0 (0)
ARIA-E	1 (2.3)	10 (22.2)
Symptomatic	0 (0)	1 (2.2)[g]
ARIA-H	5 (11.6)	16 (35.6)
Isolated ARIA-H	5 (11.6)	8 (17.8)
Microhemorrhage	4 (9.3)	11 (24.4)
Superficial siderosis	1 (2.3)	7 (15.6)

Table 4 continued

Event, *n* (%) Placebo(*N* = 43) Donanemab(*N* = 45)		
Intracerebral hemorrhage > 1 cm	0 (0)	0 (0)

AE adverse event, *ARIA-E* amyloid-related imaging abnormalities–edema/effusions, *ARIA-H* amyloid-related imaging abnormalities–hemorrhage/hemosiderin deposition, *MedDRA* Medical Dictionary for Regulatory Activities, *MRI* magnetic resonance imaging, *PT* Preferred Term, *SAE* serious adverse event, *SOC* System Organ Class, *TEAE* treatment-emergent adverse event

[a]Participants may be counted in more than one category

[b]Deaths are also included as SAEs and discontinuations due to AEs

[c]A TEAE is defined as an event that first occurred or worsened after the treatment initiation date and up to either the first visit date of the long-term extension phase − 1 day or end of treatment period in double-blind phase + 57 days, whichever occurred first

[d]Includes events that were considered related to study treatment as judged by the investigator

[e]Classified using MedDRA version 25.1

[f]ARIA and intracerebral hemorrhage > 1 cm events based on MRI or TEAE PT cluster. ARIA-E cluster: ARIA-E, brain edema, and vasogenic cerebral edema; ARIA-H cluster: ARIA-H, brain stem microhemorrhage, cerebellar microhemorrhage, cerebral hemosiderin deposition, cerebral microhemorrhage, and superficial siderosis of central nervous system; intracerebral hemorrhage > 1 cm cluster: cerebral hemorrhage and hemorrhagic stroke

[g]Symptom of confusional state

population (15.9% vs. 23.3%), further strengthening the results despite the small sample size. However, further follow-up is required to assess long-term safety and efficacy of donanemab in both the Japanese and global populations, and a 78-week, double-blind extension to TRAILBLAZER-ALZ 2 is underway. Biological factors, such as body size and genetic profile [42–45], and cultural factors, such as lifestyle, are similar between Japan and other Asian countries, especially East Asia, and these may differ from most Western countries. Therefore, extrapolation of the study findings to the broader Asian population could be applicable. However, further research in a more diverse Asian population is needed.

In conclusion, the overall efficacy, safety, and biomarker changes with donanemab in Japanese participants in the TRAILBLAZER-ALZ 2 trial were generally similar to those reported for the global population, although no direct statistical comparison was conducted. These results, together with the high rate of treatment completion, suggest that donanemab could be beneficial in the treatment of early, symptomatic AD in both the global and Japanese populations, although confirmatory research is required.

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Data Availability. Eli Lilly and Company provides access to all individual participant data collected during the trial, after anonymization, with the exception of pharmacokinetic or genetic data. Data are available to request 6 months after the indication studied has been approved in the United States and the European Union and after primary publication acceptance, whichever is later. No expiration date of data requests is currently set once data are made available. Access is provided after a proposal has been approved by an independent review committee identified for this purpose and after receipt of a signed data sharing agreement. Data and documents, including the study protocol, statistical analysis plan, clinical study report, blank or annotated case report forms, will be provided in a secure data sharing environment. For details on submitting a request, see the instructions provided at www.vivli.org.

Declaration

Conflict of Interest. Shoichiro Sato, Naohisa Hatakeyama, Hideaki Katagiri, and Shinji Fujikoshi are employees of Eli Lilly Japan K.K. and minor shareholders in Eli Lilly and Company. Sadao Katayama was an investigator in the TRAILBLAZER-ALZ 2 trial and has received lecture fees from Eli Lilly Japan K.K., Eisai Co., Ltd., and Kowa Pharmaceutical Industry Co., Ltd. John Sims is an employee of and minor shareholder in Eli Lilly and Company.

Ethical Approval. This trial was conducted according to the Declaration of Helsinki, the International Council for Harmonisation Guideline for Good Clinical Practice, and local regulatory requirements. The protocol was approved by ethics review boards at each study site. Participants and their partners provided written informed consent before any study procedures were conducted. Permission to use the Clinical Dementia Rating Scale and the Alzheimer's Disease Assessment Scale was obtained from the copyright holders before the start of the study.

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