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Amyloid-Related Imaging Abnormalities (ARIA) in Clinical Trials of Gantenerumab in Early Alzheimer Disease

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IMPORTANCE Data from 2 phase 3 studies of gantenerumab, GRADUATE I/II, and their open-label extensions represent a resource to further characterize amyloid-related imaging abnormalities (ARIA), including long-term sequelae.

OBJECTIVES To describe the characteristics of ARIA and risk factors and clinical consequences of ARIA-edema (ARIA-E).

DESIGN, SETTING, AND PARTICIPANTS Secondary data collection from the GRADUATE I/II phase 3 randomized, double-blind, placebo-controlled, 116-week parallel-group studies and their open-label extensions, including PostGraduate, with up to 210 (mean, 125) weeks of total gantenerumab treatment were conducted between 2018 and 2023. The study included multicenter trials at 288 sites across 30 countries. GRADUATE I/II enrolled 985 and 980 participants, respectively, with early symptomatic Alzheimer disease (AD) and amyloid-beta (Aβ) pathology who were aged 50 to 90 years. PostGraduate enrolled 1382 participants (671 previously randomized to gantenerumab). Data were analyzed from November 2, 2022, to October 10, 2023.

INTERVENTIONS GRADUATE I/II participants were randomized 1:1 to gantenerumab or placebo. Nine-month uptitration was used to mitigate ARIA risk.

MAIN OUTCOMES AND MEASURES Postbaseline safety monitoring, including brain magnetic resonance imaging (MRI) findings, and adverse events and cognitive assessments.

RESULTS The safety-evaluable MRI population of GRADUATE I/II comprised 1939 participants (mean age, 71.7 years; 1105 female [57.0%]). Severity of AD–related Aβ neuropathology (lower cerebrospinal fluid [CSF] Aβ42, hazard ratio [HR] for CSF Aβ42: 0.4; 95% CI, 0.2-0.7) and comorbid cerebrovascular pathology (Fazekas score: HR, 1.6; 95% CI, 1.3-2.0; total superficial siderosis count: HR, 1.9; 95% CI, 1.3-2.6; total microhemorrhage count: HR, 1.3; 95% CI, 1.0-1.5) may be important baseline risk factors for ARIA-E, in addition to apolipoprotein E (APOE) ε4 status (APOE ε4 heterozygous carrier: HR, 2.0; 95% CI, 1.4-2.8 and APOE ε4 homozygous carrier: HR, 4.7; 95% CI, 3.2-6.7). At the group level, ARIA-E did not impact long-term cognitive and functional performance (relative difference in adjusted means for Clinical Dementia Rating–Sum of Boxes was −9% in pooled GRADUATE analysis at week 116 and when censored at first ARIA-E). While taking gantenerumab, ARIA-E and ARIA-hemosiderin occurred in 24.9% (247 of 993) and 22.9% (227 of 993) participants, respectively; first ARIA-E occurred by week 64 in 86.2% (213 of 247) of participants with ARIA-E. Narratives are provided for all serious symptomatic ARIA-E cases.

CONCLUSIONS AND RELEVANCE These results show that in addition to APOE ε4 allele count, severity of Aβ neuropathology and comorbid cerebrovascular pathology may be relevant for clinicians prescribing anti-Aβ monoclonal antibodies for early AD and developing individualized safety monitoring plans. Evaluation of these risk factors in other anti-Aβ monoclonal antibodies is recommended.

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Supplemental content

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Amyloid-beta (Aβ) processing and deposition play a critical role in the Alzheimer disease (AD) pathogenesis.[1] Anti-Aβ monoclonal antibodies (mAbs) lecanemab and donanemab demonstrated significant reductions vs placebo in clinical progression of early symptomatic AD (mild cognitive impairment due to AD and mild AD) in phase 3 clinical trials, in parallel with significant Aβ plaque clearance.[2,3] These drugs are US Food and Drug Administration licensed for the treatment of early symptomatic AD.[4-6]

Amyloid-related imaging abnormalities (ARIA) comprise vasogenic edema and/or sulcal effusions (ARIA-edema [ARIA-E]; best visualized on magnetic resonance imaging [MRI] fluid-attenuated inversion recovery sequences) and microhemorrhages and/or superficial siderosis (SS) (ARIA-hemosiderin [ARIA-H]; on iron-sensitive MRI sequences, such as gradient-recalled echo/T2*-weighted or susceptibility-weighted imaging).[7,8] While ARIA may develop spontaneously in relation to AD or cerebral amyloid angiopathy (CAA), it is also the main adverse effect of anti-Aβ mAbs (absolute rates vary between molecules)[2,3,9-15] and was reported for a microglial-receptor triggering receptor expressed on myeloid cells 2-binding mAb in AD.[16] ARIA pathophysiology hypotheses include Aβ clearance-related temporarily increased cerebral vascular permeability[10,12]; reactive immune cell-mediated inflammation,[17] and complement cascade activation by anti-Aβ mAb-vascular Aβ complexes.[18]

Since ARIA represents a class effect of first-generation anti-Aβ mAbs, understanding ARIA risk factors and symptomatology may inform future clinical decision-making and MRI monitoring. It is also important for ensuring individuals with AD are informed of anti-Aβ mAbs risks.

Key efficacy and safety outcomes from 2 global phase 3 gantenerumab studies, GRADUATE I and II (NCT03444870/NCT03443973), and their open-label rollover studies, including PostGraduate (NCT04374253), have been reported previously.[19-21] Although gantenerumab was not associated with a significant reduction in clinical decline in participants with early AD (difference in Clinical Dementia Rating–Sum of Boxes [CDR-SB] at week 116 vs placebo: GRADUATE I, −0.31; 95% CI, −0.66 to 0.05 and GRADUATE II, −0.19; 95% CI, 0.55-0.17; favoring gantenerumab), these studies provide a rich resource to further characterize ARIA and its longer-term consequences.[22] While in GRADUATE I/II incidence of ARIA-H was higher in gantenerumab than placebo arms, incidence of new isolated ARIA-H was comparable,[22] similar to observations for other in-class mAbs[3,13]; the higher incidence of ARIA-H in the active arms is driven by ARIA-H concurrent with ARIA-E. As such, while we report key ARIA-H characteristics, we focus on the risk factors, descriptive characteristics, and clinical consequences of ARIA-E.

Key Points

Question What are the risk factors for, characteristics of, and clinical consequences of amyloid-related imaging abnormalities-edema (ARIA-E) in phase 3 trials of gantenerumab in early Alzheimer disease (AD)?

Findings Severity of amyloid-beta (Aβ) neuropathology and comorbid cerebrovascular pathology may be important baseline risk factors for ARIA-E, in addition to apolipoprotein E ε4. ARIA-E had no long-term impact on cognitive/functional scale performance in most participants.

Meaning These results demonstrate that clinicians may wish to consider potential risk factors for ARIA-E (eg, severity of Aβ neuropathology and comorbid cerebrovascular pathology) when prescribing anti-Aβ monoclonal antibodies for early AD and developing individualized safety monitoring plans.

Methods

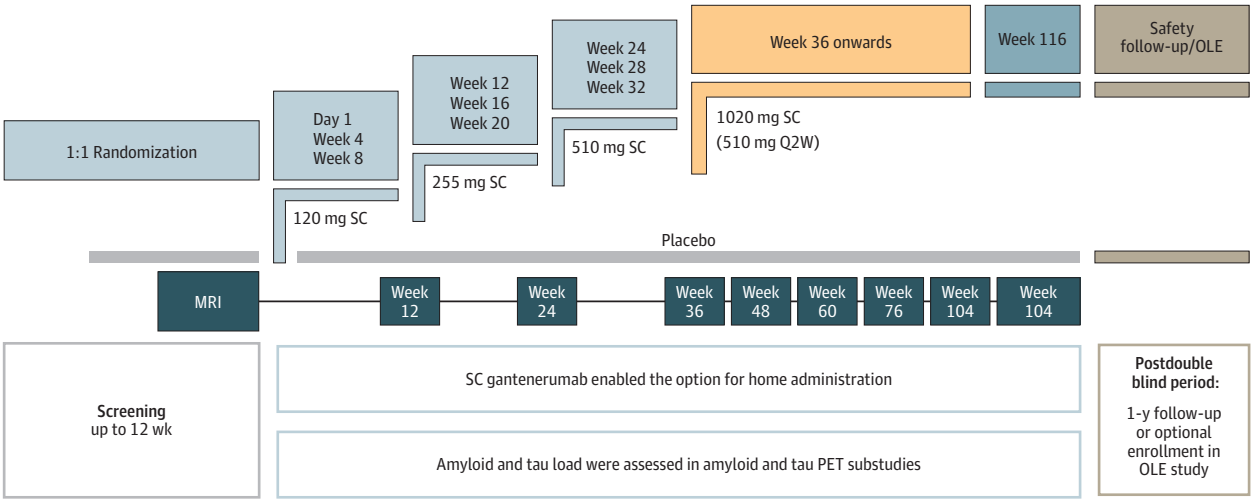
The design of the identical phase 3 randomized, double-blind, placebo-controlled, parallel-group GRADUATE I and II trials has been previously published.[22] Briefly, GRADUATE I and II enrolled 985 and 980 participants, respectively, with early symptomatic AD and confirmed Aβ pathology who were aged 50 to 90 years. More than 5 microhemorrhages and/or focal SS areas (though also more than 3 focal SS areas), overall Fazekas score of 3, and anticoagulation constituted exclusion criteria. Single- or dual-antiplatelet therapy was allowed. PostGraduate (NCT04374253) was an open-label, multicenter, rollover study evaluating the long-term safety, tolerability, and efficacy of gantenerumab in participants from the GRADUATE I/II trials. Trial conduct followed the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use E6 guideline for Good Clinical Practice and the Declaration of Helsinki and applicable laws and regulations. An independent data monitoring committee provided oversight. All trial participants provided written informed consent.

In GRADUATE I/II, participants were randomized 1:1 to subcutaneously administered gantenerumab or placebo for up to 116 weeks with a 9-month uptitration regimen to the 510-mg every 2 weeks target dose to mitigate dose-dependent ARIA risk.[23,24] Safety MRIs were performed at baseline, prior to each dose uptitration, regularly on target dose, and as determined by investigators and evaluated by a single central neuroradiologist (**Figure 1**). ARIA dosing intervention rules are provided in eFigure 1 in Supplement 1. Participants followed an identical dosing regimen and MRI frequency regardless of APOE ε4 status. ARIA-E radiological severity was determined using Barkhof Grand Total Score ([BGTS] range, 0-60).[25]

After 116 weeks of double-blind treatment, eligible participants could receive open-label gantenerumab, initiated under the GRADUATE protocol or after directly entering PostGraduate (eFigure 2 in Supplement 1) with up to 210 (mean, 125) weeks of gantenerumab treatment in participants randomized to gantenerumab in the double-blind phase. Otherwise, 14- and 50-week postdosing follow-up was required.

Safety outcomes included adverse events (AEs), serious AEs, and MRI findings. Since only selected ARIA MRI findings were reportable as AEs (ie, symptomatic, leading to dosing intervention, or otherwise clinically significant), ARIA analyses reported are based on the MRI safety-evaluable dataset. Symptomatic ARIA-E was defined by central nervous sys-

Figure 1. GRADUATE I and II: Study Drug Dosing Regimen and Routine Magnetic Resonance Imaging (MRI) Schedule



OLE indicates open-label extension; PET, positron emission tomography; Q2W, every 2 weeks; SC, subcutaneous.

tem (CNS) AE(s) temporally associated with ARIA-E MRI findings, regardless of the investigator's causality attribution.

Efficacy scales, including CDR-SB, the Alzheimer's Disease Assessment Scale, Cognition Subscale 13 (ADAS-Cog13), Alzheimer's Disease Cooperative Study Group Activities of Daily Living (ADCS-ADL), and Functional Activities Questionnaire (FAQ), and amyloid positron emission tomography, volumetric MRI, and plasma and cerebrospinal fluid (CSF) biomarkers were collected and reported. Measures were implemented to mitigate ARIA-related bias in efficacy assessments.[22]

Statistical Analysis

As GRADUATE I/II were identically designed with efficacy and safety results concordant,[22] the pooled dataset from the double-blind study periods was used that included all participants who received at least 1 study drug dose, followed by at least 1 MRI (safety-evaluable MRI population). Post-baseline data covered the double-blind period from the first study drug dose up to 14 weeks after the last dose, but no later than the day before the first open-label gantenerumab dose for participants who entered the open-label period. Data from the open-label period and PostGraduate were used to repeat the assessment of time to first ARIA-E event in participants in the gantenerumab arm in the double-blind period. Analyses were prespecified in a statistical analysis plan, except the analyses of baseline risk factors. Additional descriptive ARIA analyses are provided beyond those reported previously,[22] including stratification by APOE ε4 allele count or baseline microhemorrhage/SS presence. We used SAS version 9.4 (SAS Institute) r 4.3.1 (The R Project for Statistical Computing) for analysis.

For the analysis of risk factors for ARIA-E/ARIA-E with temporally concurrent new ARIA-H, a broad set of baseline variables for testing was developed (eMethods in Supplement 1). For the assessment of the long-term impact of ARIA-E on CDR-SB (pooled GRADUATE dataset, reported previously by study[17]), ADAS-Cog13, ADCS-ADL, and FAQ, a mixed-effect model of repeated measures was used, with all outcome data included as well as with outcome data censored upon first ARIA-E.

Results

The safety-evaluable MRI population of the GRADUATE trials comprised 1939 participants (placebo, 946; gantenerumab, 993). Baseline characteristics were comparable between treatment groups, with a mean age of 71.7 (SD, 7.7) years (eTable 1 in Supplement 1). Most participants were female (1105 of 1939 [57.0%]), had mild cognitive impairment (1062 of 1939 [54.8%]), and received symptomatic AD treatment (1240 of 1939 [64.0%]). Half of the participants were heterozygous APOE ε4 carriers (964 of 1939 [49.7%]), followed by noncarriers (645 of 1939 [33.3%]) and homozygous carriers (330 of 1939 [17.0%]). At baseline, 97 of 993 participants (9.8%) in the gantenerumab arm had microhemorrhages and/or SS (80 of 993 [8.1%] had 1 to 5 microhemorrhages and 25 of 993 [2.5%] 1 to 3 focal areas of SS). Participant flow and baseline demographics/characteristics for PostGraduate are provided in eFigure 3 and eTable 2 in Supplement 1.

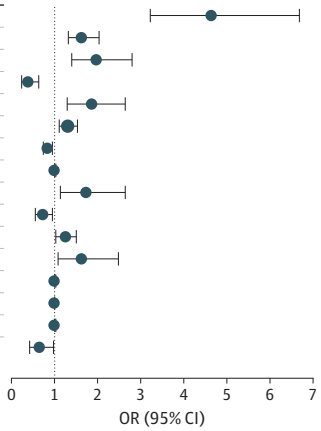
In univariate models, higher APOE ε4 allele number, higher Fazekas score, and lower CSF Aβ42 were associated with increased risk of ARIA-E (**Figure 2**A and B) and ARIA-E with concurrent ARIA-H (Figure 2C), and remained significant following Bonferroni correction. In proportional hazards modeling, higher number of SS at baseline was associated with higher risk of ARIA-E (Figure 2A). In models of ARIA-E with concurrent new ARIA-H, larger baseline numbers of microhemorrhages and/or SS and microhemorrhages alone were associated with increased risk (Figure 2C; descriptive statistics for all 57 potential baseline risk factors in eTable 3 in Supplement 1).

Multivariate models were built from variables with an unadjusted *P* value of less than .05 to optimize model fit; retained variables contain additional information on ARIA-E risk

Figure 2. Risk Factors for Amyloid-Related Imaging Abnormalities-Edema: Univariate Analyses for Baseline Variables

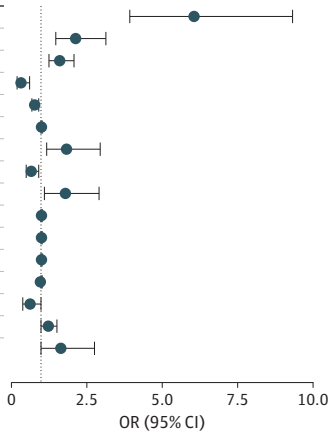
A Cox regression: risk factors for ARIA-E

	HR (95% CI)	*P* value (adjusted *P* value)
APOE ε4 homozygous carrier	4.65 (3.23-6.70)	<.001 (<.001)
Fazekas score at screening	1.65 (1.32-2.05)	<.001 (.01)
APOE ε4 heterozygous carrier	1.98 (1.40-2.80)	<.001 (.01)
CSF Aβ42 (LT)	0.40 (0.25-0.65)	<.001 (.02)
Total SS	1.86 (1.31-2.64)	.001 (.04)
Total microhemorrhages and SS	1.31 (1.12-1.53)	.001 (.05)
Volumetric MRI-total hippocampus	0.85 (0.76-0.95)	.004 (.26)
Volumetric MRI-whole brain	1.00 (1.00-1.01)	.01 (.41)
Dyslipidemia	1.74 (1.14-2.64)	.01 (.70)
Male sex	0.73 (0.56-0.95)	.02 (1.00)
Total microhemorrhages	1.25 (1.04-1.51)	.02 (1.00)
CSF phosphorylated tau (LT)	1.64 (1.08-2.48)	.02 (1.00)
Volumetric MRI-cortical grey matter	1.00 (1.00-1.01)	.03 (1.00)
Systolic blood pressure (mm Hg)	1.01 (1.00-1.02)	.03 (1.00)
Amyloid PET (centiloid)	1.01 (1.00-1.01)	.03 (1.00)
Diabetes	0.65 (0.43-1.00)	.05 (1.00)



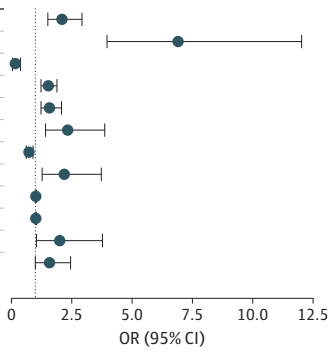
B Logistic regression: risk factors for ARIA-E

	OR (95% CI)	*P* value (adjusted *P* value)
APOE ε4 homozygous carrier	6.05 (3.93-9.31)	<.001 (<.001)
APOE ε4 heterozygous carrier	2.14 (1.47-3.13)	<.001 (.01)
Fazekas score at screening	1.62 (1.26-2.07)	<.001 (.01)
CSF Aβ42 (LT)	0.34 (0.18-0.62)	<.001 (.03)
Volumetric MRI-total hippocampus	0.80 (0.70-0.91)	.001 (.06)
Volumetric MRI-whole brain	1.00 (1.00-1.01)	.002 (.16)
Dyslipidemia	1.85 (1.17-2.94)	.01 (.60)
Male sex	0.68 (0.51-0.92)	.01 (.77)
CSF phosphorylated tau (LT)	1.80 (1.12-2.91)	.02 (1.00)
Volumetric MRI-cortical grey matter	1.01 (1.00-1.01)	.02 (1.00)
Systolic blood pressure (mmHg)	1.01 (1.00-1.02)	.03 (1.00)
Amyloid PET (centiloid)	1.01 (1.00-1.01)	.03 (1.00)
Weight (kg)	0.99 (0.98-1.00)	.04 (1.00)
Diabetes	0.62 (0.39-0.98)	.04 (1.00)
Total microhemorrhages and SS	1.23 (1.01-1.51)	.04 (1.00)
CSF total tau (LT)	1.67 (1.00-2.77)	.05 (1.00)



C Logistic regression: risk factors for ARIA-E with concurrent new ARIA-H

	OR (95% CI)	*P* value (adjusted *P* value)
Fazekas score at screening	2.12 (1.54-2.92)	<.001 (<.001)
APOE ε4 homozygous carrier	6.93 (3.99-12.04)	<.001 (<.001)
CSF Aβ42 (LT)	0.18 (0.08-0.42)	<.001 (.004)
Total microhemorrhages and SS	1.55 (1.25-1.91)	<.001 (.004)
Total microhemorrhages	1.62 (1.25-2.09)	<.001 (.01)
Presence of microhemorrhage(s) and/or SS	2.35 (1.42-3.88)	.001 (.06)
Volumetric MRI-total hippocampus	0.76 (0.65-0.90)	.002 (.10)
APOE ε4 heterozygous carrier	2.22 (1.31-3.76)	.003 (.20)
Amyloid PET (centiloid)	1.01 (1.00-1.02)	.02 (1.00)
Volumetric MRI -cortical grey matter	1.01 (1.00-1.01)	.02 (1.00)
CSF phosphorylated tau (LT)	2.02 (1.08-3.80)	.03 (1.00)
Total SS	1.59 (1.01-2.50)	.04 (1.00)



All the variables are measured at baseline unless indicated otherwise. Univariate analyses for baseline variables with an unadjusted *P* value of less than .05. Apolipoprotein E (APOE) ε4, dyslipidemia, sex, diabetes, and presence of amyloid-related imaging abnormalities-hemosiderin are treated as categorical variables with associated reference levels of APOE ε4 noncarrier, no dyslipidemia, female, no diabetes, and absent. Aβ indicates amyloid-beta; CSF, cerebrospinal fluid; HR, hazard ratio; LT, log 2 transformed; MRI, magnetic resonance imaging; OR, odds ratio; PET, positron emission tomography; SS, superficial siderosis.

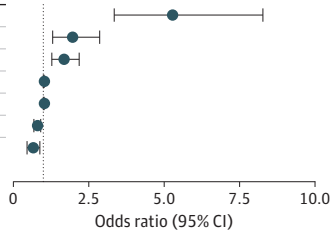
relative to other variables in the model. Variables remaining in multivariate models of ARIA-E risk following stepwise selection are shown in **Figure 3**. For multivariate model results for ARIA-E with concurrent ARIA-H, see eTable 4 in Supplement 1.

In the GRADUATE gantenerumab dataset, ARIA-E and ARIA-H occurred in 247 of 993 (24.9%) and 227 of 993 (22.9%) participants, respectively.[22] Overall incidences of ARIA-E and symptomatic ARIA-E at the study-population level increased with the APOE ε4 count.[22] This pattern was

Figure 3. Multivariate Modeling With Stepwise Logistic Regression for Baseline Variables

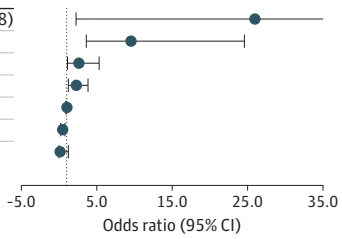
A Clinical and MRI variables and plasma biomarkers model

	OR (95% CI)
APOE ε4 homozygous carrier	5.25 (3.34-8.25)
APOE ε4 heterozygous carrier	1.93 (1.31-2.85)
Fazekas score at screening	1.67 (1.28-2.18)
Systolic blood pressure (mm Hg)[a]	1.01 (1.00-1.02)
Volumetric MRI-whole brain (mL)	1.00 (1.00-1.01)
Volumetric MRI- total hippocampus (mL)	0.79 (0.68-0.92)
Male sex	0.63 (0.46-0.87)



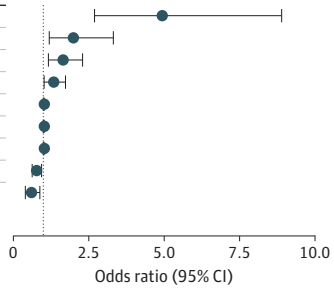
B Clinical and MRI variables and plasma + CSF biomarkers model

	OR (95% CI)
CSF phosphorylated tau (LT)	25.86 (2.28-293.78)
APOE ε4 homozygous carrier	9.45 (3.63-24.58)
APOE ε4 heterozygous carrier	2.50 (1.18-5.27)
Fazekas score at screening	2.20 (1.24-3.89)
Weight (kg)	0.96 (0.94-0.99)
CSF Aβ42 (LT)	0.36 (0.17-0.74)
CSF total tau (LT)	0.10 (0.01-1.20)



C Clinical and MRI variables and plasma + amyloid PET biomarkers model

	OR (95% CI)
APOE ε4 homozygous carrier	4.90 (2.70-8.89)
APOE ε4 heterozygous carrier	1.99 (1.20-3.31)
Fazekas score at screening	1.63 (1.16-2.30)
Total microhemorrhages and SS	1.33 (1.01-1.74)
Systolic blood pressure (mm Hg)	1.01 (1.00-1.03)
Amyloid PET (centiloid)	1.01 (1.00-1.02)
Volumetric MRI	1.00 (1.00-1.01)
Volumetric MRI	0.77 (0.63-0.94)
Male sex	0.60 (0.40-0.90)



Apolipoprotein E (APOE) ε4 and sex are treated as categorical variables with APOE ε4 noncarrier and female as the reference levels. In addition to those meeting criteria for univariate significance, hippocampal volume, whole-brain volume, systolic blood pressure, and sex were retained in multivariate models of amyloid-related imaging abnormalities-edema risk. In models containing cerebrospinal fluid (CSF) measures, CSF pTau, CSF tTau, and weight were also retained; whereas in amyloid positron emission tomography (PET) models, amyloid PET centiloid, and total number of amyloid-related imaging abnormalities-hemosiderin remained in multivariate models. OR indicates odds ratio.

[a]Per 1 mm Hg; per 10 mm Hg, the OR would be 1.1.

also observed for ARIA-E with new concurrent ARIA-H and recurrent ARIA-E (**Table 1**). However, within individuals who developed ARIA-E, there was no association between the number of APOE ε4 copies and symptomatic or serious symptomatic ARIA-E rate. The characteristics of serious symptomatic ARIA-E cases are presented in eTable 5 and eMethods in Supplement 1.

In the double-blind period of the GRADUATE trials, the mean time to first ARIA-E in gantenerumab-treated participants was 35.7 (SD, 13.0) weeks and 49.2 (SD, 21.4) weeks in participants with and without baseline microhemorrhages and/or SS, respectively. A numerically shorter time to first ARIA-E onset and increased mean radiological severity, resolution time, and likelihood of recurrence in those who had an opportunity for recurrence (ie, initial episode's resolution followed by gantenerumab dosing and MRI) were observed in APOE ε4 homozygotes compared with noncarriers and heterozygotes (Table 1). In those who developed ARIA-E, homozygotes were more likely to develop concurrent microhemorrhages but not SS compared with heterozygotes and noncarriers (Table 1). Most gantenerumab-treated participants with ARIA-E had their first ARIA-E episode by week 64 (213 of 247 [86.2%]). However, first ARIA-E occurred up to week 116 and, including the open-label period, first ARIA-E occurred up to week 168, albeit at lower incidence than in the double-blind period (eFigures 4 through 7 in Supplement 1 including by APOE ε4 stratifications).

In the GRADUATE gantenerumab dataset, concurrent new ARIA-H was reported for 142 of 324 participants (43.8%) with asymptomatic ARIA-E and 36 of 56 (64.3%) with symptomatic ARIA-E. The mean radiological ARIA-E severity of the most severe episode per participant in BGTS was 9.0 (SD, 6.7), 17.5 (SD, 12.0), and 21.3 (SD, 8.3) for asymptomatic, nonserious symptomatic, and serious symptomatic ARIA-E, respectively. Of participants with ARIA-E who had an opportunity for ARIA-E recurrence in the double-blind period, 15 of 21 (71.4%) with and 80 of 173 (46.2%) without baseline microhemorrhages and/or SS had recurrent ARIA-E.

In gantenerumab-treated participants in the double-blind period who had recurrent ARIA-E, the mean radiological severity of the first ARIA-E was 9.8 (SD, 7.8) vs 9.3 (SD, 7.1) for the second ARIA-E episode. There was no evidence for a change in symptomatic status between first and second ARIA-E episode (eTable 6 in Supplement 1).

Table 1. Selected Descriptive Characteristics of Amyloid-Related Imaging Abnormalities (ARIA) Magnetic Resonance Imaging (MRI) Findings by Apolipoprotein E (APOE) ε4 Status

MRI findings by APOE genotype	No. (%) of participants					
	Placebo (n = 946)			Gantenerumab (n = 993)		
	APOE ε4 noncarrier (n = 310)	APOE ε4 heterozygous (n = 486)	APOE ε4 homozygous (n = 150)	APOE ε4 noncarrier (n = 335)	APOE ε4 heretozygous (n = 478)	APOE ε4 homozygous (n = 180)
ARIA-E						
ARIA-E MRI findings by APOE genotype						
Total[a]	9 (2.9)	10 (2.1)	7 (4.7)	44 (13.1)	117 (24.5)	86 (47.8)
No. of episodes	10	11	8	66	170	144
Symptomatic ARIA-E						
Total[b,a]	1 (0.3)	1 (0.2)	0 (0)	13 (3.9)	18 (3.8)	19 (10.6)
Those with ARIA-E	1/9 (11.1)	1/10 (10.0)	0/7 (0)	13/44 (29.5)	18/117 (15.4)	19/86 (22.1)
Serious symptomatic ARIA-E						
Total[b,c]	0 (0)	0 (0)	0 (0)	6 (1.8)	2 (0.4)	3 (1.7)
Those with ARIA-E	0/9 (0)	0/10 (0)	0/7 (0)	6/44 (13.6)	2/117 (1.7)	3/86 (3.5)
ARIA-E with concurrent new ARIA-H[d]						
Total	1 (0.3)	4 (0.8)	2 (1.3)	20 (6.0)	59 (12.3)	55 (30.6)
Those with ARIA-E	1/9 (11.1)	4/10 (40.0)	2/7 (28.6)	20/44 (45.5)	59/117 (50.4)	55/86 (64.0)
ARIA-E with concurrent new microhemorrhage[d]						
Total	1 (0.3)	2 (0.4)	0 (0.0)	17 (5.1)	43 (9.0)	50 (27.8)
Those with ARIA-E	1/9 (11.1)	2/10 (20.0)	0/7 (0)	17/44 (38.6)	43/117 (36.8)	50/86 (58.1)
ARIA-E with concurrent new superficial siderosis[d]						
Total	1 (0.3)	2 (0.4)	2 (1.3)	14 (4.2)	38 (7.9)	25 (13.9)
Those with ARIA-E	1/9 (11.1)	2/10 (20.0)	2/7 (28.6)	14/44 (31.8)	38/117 (32.5)	25/86 (29.1)
Recurrent ARIA-E						
Total	1 (0.3)	1 (0.2)	1 (0.7)	14 (4.2)	40 (8.4)	41 (22.8)
Those with ARIA-E at risk of recurrence	1/6 (16.7)	1/7 (14.3)	1/7 (14.3)	14/30 (46.7)	40/98 (40.8)	41/66 (62.1)
Time to onset of first ARIA-E, mean (SD), wk	59.4 (39.7)	60.9 (34.8)	49.6 (35.9)	49.6 (25.6)	48.8 (20.7)	45.1 (19.0)
Radiological severity of all ARIA-E episodes (BGTS)						
Mean (SD)	3.8 (3.8)	4.2 (2.9)	2.9 (2.2)	8.5 (7.9)	7.9 (6.1)	10.5 (8.8)
ARIA-E episodes of severity ≥4[e]	3/10 (30.0)	5/11 (45.5)	3/8 (37.5)	46/66 (69.7)	131/170 (77.1)	116/144 (80.6)
Resolution time of all ARIA-E episodes						
No. all resolved ARIA-E episodes	10	10	8	62	164	139
Mean resolution time (SD), wk	8.7 (7.1)	8.8 (4.7)	4.4 (1.5)	10.9 (7.3)	10.3 (8.2)	13.0 (9.7)
Median resolution time, wk	5.9	8.0	4.0	8.6	8.3	11.7
ARIA-H						
Any new ARIA-H MRI findings by APOE genotype						
No. (%)	31 (10)	61 (12.6)	24 (16.0)	58 (17.3)	95 (19.9)	74 (41.1)
Mean No. of new findings (SD)	1.8 (2.8)	1.7 (1.3)	1.9 (1.4)	4.4 (6.8)	4.3 (5.3)	9.9 (15.1)
Median No. of new findings	1.0	1.0	1.0	2.0	2.0	5.0

(continued)

Table 1. Selected Descriptive Characteristics of Amyloid-Related Imaging Abnormalities (ARIA) Magnetic Resonance Imaging (MRI) Findings by Apolipoprotein E (APOE) ε4 Status (continued)

MRI findings by APOE genotype	No. (%) of participants					
	Placebo (n = 946)			Gantenerumab (n = 993)		
	APOE ε4 noncarrier (n = 310)	APOE ε4 heterozygous (n = 486)	APOE ε4 homozygous (n = 150)	APOE ε4 noncarrier (n = 335)	APOE ε4 heretozygous (n = 478)	APOE ε4 homozygous (n = 180)
Any new microhemorrhage						
No. (%)	27 (8.7)	49 (10.1)	18 (12.0)	47 (14.0)	71 (14.9)	67 (37.2)
Mean No. of new findings (SD)	1.7 (1.8)	1.5 (1.0)	2.0 (1.5)	3.4 (6.3)	3.6 (5.0)	9.3 (15.8)
Median No. of new findings	1.0	1.0	1.0	1.0	2.0	4.0
Any new superficial siderosis						
No. (%)	5 (1.6)	16 (3.3)	8 (5.3)	25 (7.5)	54 (11.3)	37 (20.6)
Mean No. of new findings (SD)	2.2 (2.7)	1.7 (1.5)	1.3 (0.5)	3.8 (4.0)	2.8 (2.8)	3.1 (1.9)
Median No. of new findings	1.0	1.0	1.0	2.0	2.0	3.0

Abbreviations: ARIA-E, amyloid-related imaging abnormalities-edema; ARIA-H, amyloid-related imaging abnormalities-hemosiderin; BGTS, Barkhof Grand Total Score.

[a] Reported previously.[17]

[b] Symptomatic ARIA-E was defined as ARIA-E temporally associated with central nervous system symptoms.

[c] Serious symptomatic ARIA-E was defined as ARIA-E associated with central nervous system symptoms where the ARIA-E adverse event and/or the central nervous system symptom adverse event was reported as a serious adverse event.

[d] ARIA-E and ARIA-H concurrence was defined as temporal co-occurrence, with new ARIA-H MRI finding(s) detected at the time of emerging or continuing ARIA-E MRI finding(s).

[e] BGTS 4 or higher was the protocol-mandated threshold for study drug dosing suspension; dosing could continue if ARIA-E event was BGTS less than 4 and asymptomatic.

Table 2. GRADUATE I and II: Adjusted Mean Changes From Baseline and Differences in Selected Efficacy Scales

Efficacy scale	Overall at wk 116				Censored at time of first ARIA-E			
	Adjusted mean (SE) [No.]		Difference in adjusted means (SE)	Relative difference in adjusted means (%)	Adjusted mean (SE) [No.]		Difference in adjusted means (SE)	Relative difference in adjusted means (%)
	Placebo	Gantenerumab			Placebo	Gantenerumab		
CDR-SB	3.3 (0.1) [752]	3.0 (0.1) [728]	−0.3 (0.1)	−9	3.3 (0.1) [733]	3.0 (0.1) [562]	−0.3 (0.2)	−9
ADAS-Cog13	8.8 (0.3) [730]	7.4 (0.3) [707]	−1.4 (0.5)	−15	8.8 (0.3) [711]	7.7 (0.4) [544]	−1.1 (0.5)	−12
ADCS-ADL	−10.8 (0.4) [751]	−9.8 (0.4) [729]	1.1 (0.6)	10	−10.8 (0.4) [733]	−9.9 (0.5) [561]	0.9 (0.7)	9
FAQ	7.4 (0.2) [749]	6.5 (0.2) [n = 726]	−0.9 (0.3)	−13	7.4 (0.2) [732]	6.7 (0.3) [560]	−0.7 (0.3)	−10

Abbreviations: ADAS-Cog13, Alzheimer Disease Assessment Scale—Cognitive Subscale 13; ADCS-ADL, Alzheimer Disease Cooperative Study—Activities of Daily Living; ARIA-E, amyloid-related imaging abnormalities-edema; CDR-SB, Clinical Dementia Rating—Sum of Boxes; FAQ, Functional Activities Questionnaire.

Of gantenerumab-treated participants, 11 of 993 had serious symptomatic ARIA-E (1%). The most common symptoms were confusion, headache, and aphasia; less common symptoms included seizures and status epilepticus (eTable 5 in Supplement 1). Eight of 11 participants were treated with corticosteroids. None received thrombolytics. There were no ARIA-related fatalities. Summaries for all participants who experienced serious symptomatic ARIA-E (involving hospitalization) are reported in the eMethods in Supplement 1. APOE ε4 status did not substantially impact the incidence of serious symptomatic ARIA-E (Table 1).

In the GRADUATE dataset, at week 116, comparable results were observed from models including all available efficacy measure outcome data vs models where available outcome data were censored at first ARIA-E, as measured by difference and relative difference in adjusted means on any of the efficacy scales tested (**Table 2**).

Discussion

ARIA is an important adverse effect of anti-Aβ mAbs tested in AD, including gantenerumab,[2,3,9-13] with some of these agents available in clinical practice for the treatment of early symptomatic AD.[4]

Reports describing and characterizing ARIA with anti-Aβ mAbs have previously been published.[13,26-28] As noted in the Introduction, findings from studies of gantenerumab and other in-class mAbs suggest that the imbalance in ARIA-H between active treatment and placebo arms is driven by ARIA-H co-

occurring with ARIA-E.[3,13,22] For this reason, we focused on the risk factors, descriptive characteristics, and clinical consequences of ARIA-E associated with gantenerumab treatment in the GRADUATE studies.

Higher anti-Aβ mAb dose, increased number of APOE ε4 alleles, and microhemorrhage presence are well established as nonmodifiable baseline risk factors for ARIA-E.[7,13,29-33] Analyses of the GRADUATE dataset, including 57 baseline variables of interest—to our knowledge, the broadest published set of baseline variables assessed—confirmed the increasing APOE ε4 number as a significant baseline ARIA-E risk factor. Additionally, the number of SS, higher Fazekas score, and lower CSF Aβ42 emerged as potential baseline risk factors for ARIA-E. Total microhemorrhage and SS number, higher amyloid burden on positron emission tomography, more cardiovascular risk factors, lower hippocampal volume, female sex, and higher CSF phosphorylated tau showed some association that, while not statistically significant when corrected for multiple comparisons, should be explored further. Overall, these findings suggest that severity of AD amyloid-related neuropathology (lower CSF Aβ42)[34] and comorbid cerebrovascular pathology (Fazekas score, total SS, and total microhemorrhage counts) may be important ARIA-E risk factors in addition to APOE ε4 number.

Multiple mechanisms have been proposed to explain the association between the APOE ε4 allele and increased ARIA-E risk: (1) reduced cerebrovascular integrity, (2) increased neuroinflammation and immune dysregulation, and (3) elevated levels of CAA.[35] Total SS is also associated with CAA,[36] while white matter hyperintensities may reflect reduced cerebrovascular integrity[37] or CAA, particularly when in a multispot pattern,[36] suggesting these risk factors mediate ARIA risk through shared mechanisms.

Increasing number of APOE ε4 alleles was also associated with higher incidence of ARIA-E with new ARIA-H. Numerically shorter time to first ARIA-E onset and increased mean radiological severity, resolution time, and likelihood of recurrence (in those with a recurrence opportunity) were observed in APOE ε4 homozygotes compared with heterozygotes and noncarriers; apart from similar findings for donanemab concerning ARIA-E radiological severity,[2] these associations between ARIA-E characteristics and number of ε4 copies have not been published for other mAbs. The apparent lack of impact of 1 APOE ε4 copy on these ARIA-E features vs the potential impact of 2 APOE ε4 copies requires further investigation.

Approximately 1 in 5 individuals with ARIA-E had temporally associated CNS symptoms, most commonly headache and dizziness.[22] Although incidence of any ARIA-E and symptomatic ARIA-E increased with APOE ε4 allele count, despite APOE ε4 allele count being associated with greater radiological severity, among individuals who developed ARIA-E, there was a similar rate of symptomatic cases across APOE ε4 allele counts. Notably, two-thirds of symptomatic ARIA-E events, about 50% more than of asymptomatic ARIA-E events, co-occurred with new ARIA-H. However, greater radiological severity of symptomatic ARIA-E, and ARIA-E with concurrent new ARIA-H (eTable 7 in Supplement 1) makes it difficult to determine whether the relationship with symptomatology is directly or indirectly related to greater radiological severity.

The specific ARIA incidence varies between anti-Aβ mAbs (ARIA-E, 13% to 35% and symptomatic ARIA-E, 3% to 9%; ARIA-H microhemorrhage, 14% to 27% and SS, 6% to 16%)[2,3,13,22] due to intrinsic molecular characteristics, targeted amyloid species, trial designs, and population characteristics, including baseline amyloid positron emission tomography burden and distribution, or definition of symptomatic ARIA-E. However, generally similar patterns regarding rates according to APOE ε4 status, rates of symptomatic ARIA-E within overall ARIA-E rates, or imbalances in ARIA-H driven by those with ARIA-E have been reported for these mAbs, including gantenerumab.[2,3,13,15,22]

Most gantenerumab-treated participants with ARIA-E had their first ARIA-E episode within 16 months of initiating gantenerumab; however, first ARIA-E cases also occurred much later, up to 42 months from treatment initiation. This was later than for other mAbs[5,6,13,15,38] and unexpected based on previous open-label studies with a similar gantenerumab dosing regimen[39] and could be due to the longer titration period and slower and lower than predicted Aβ removal in the GRADUATE studies. Baseline microhemorrhages and/or SS were associated with an approximately 3-month earlier onset of first ARIA-E.

Radiological ARIA-E severity on gantenerumab was approximately 2 times higher in participants with CNS symptoms than in those without and higher with serious than nonserious symptomatic ARIA-E. However, there also was a significant overlap between the groups and large variability in radiological-clinical relationship, with some radiologically severe ARIA-E cases remaining asymptomatic. Further work is required to understand the relationship between radiological features and symptomatology, including lesion location. Radiological severity did not increase in recurrent events, although this analysis carries a risk for retention bias.

There was no evidence for ARIA-E impact on longitudinal cognitive (CDR-SB, ADAS-Cog13) and functional (ADCS-ADL, FAQ) outcomes at the group level, supporting that ARIA-E do not generally result in long-term detrimental effects on cognition or function. However, ARIA-E might have long-term sequelae in individual cases (eMethods in Supplement 1). For example, in a participant who experienced a serious symptomatic ARIA-E, a residual significant decline in activities of daily living following ARIA-E resolution was considered by the investigator as a potential ARIA-E sequela, albeit confounded by significant Mini-Mental State Examination decline trajectory that started before ARIA-E onset. The lack of impact of APOE ε4 status on serious symptomatic ARIA-E incidence in this series differs from other reports with serious events primarily in APOE ε4 carriers[2,40] and may be due to the limited number of serious events.

While serious symptomatic ARIA-E remains understudied due to its relative rarity, to our knowledge, ours is the first publication that provides case narratives for 11 such cases (eMethods in Supplement 1). Several of the cases presented with temporal focal neurologic deficits. Since the initial workup in individuals on anti-Aβ mAbs exhibiting such symptoms may focus on and lead to an inadvertent diagnosis of suspected is-

chemic stroke and treatment with thrombolytics, it is critical that emergency clinicians are aware that patients are receiving an Aβ-lowering antibody, ARIA is an important differential diagnosis, computed tomography is insensitive in detecting ARIA and MRI is required, and use of thrombolytics should be restricted unless ARIA is excluded. Although GRADUATE I/II were not designed to assess the safety of a treatment rechallenge post-ARIA, treatment reintroduction following severe radiological/symptomatic ARIA should be considered carefully.

Limitations

Limitations of our study include the unknown generalizability of our findings to a real-world early symptomatic AD population given the underrepresentation of racial and ethnic minorities and exclusion of certain individuals (eg, with more than 5 microhemorrhages and/or focal SS areas, though also more than 3 focal SS areas, significant white matter pathology, unstable or clinically significant cardiovascular disease, individuals on anticoagulation) from GRADUATE I/II. The number of symptomatic and serious symptomatic ARIA-E events is low; therefore, conclusions should be interpreted cautiously. Time to first ARIA-E-event analyses relied on routine MRI time points (although investigators could perform unscheduled MRIs), which might lead to delayed recording of ARIA-E onset. Additionally, PostGraduate was terminated early after the GRADUATE studies missed their primary end point. ARIA-E severity was expressed in BGTS because that determined clinical actions in the GRADUATE trials, but BGTS does not map 1:1 to other scales.[41] Although ARIA is a class effect of first-generation anti-Aβ mAbs, these findings should be considered molecule specific and requiring further evaluation for other in-class molecules, particularly concerning ARIA-E baseline risk factors.

While gantenerumab lacked sufficient clinical benefit for continued development, Roche is developing trontinemab, a novel, distinct monoclonal antibody. Trontinemab uses a Brainshuttle technology to gain enhanced brain access via transferrin receptor 1-mediated transcytosis at the capillary level, in combination with a gantenerumab-derived immunoglobulin G framework as an anti-Aβ binder.[42] It is hypothesized that the ability to use low doses and to deliver the therapy more directly into the brain parenchyma may result in additional safety benefits, such as reduced ARIA risk. This is supported by preliminary results from an ongoing phase 1b/2a study (NCT04639050) suggesting rapid and robust amyloid lowering by trontinemab with low ARIA incidence.[43]

Conclusions

Data from 1939 participants in 2 phase 3 studies with gantenerumab in early symptomatic AD allowed for characterization of ARIA-E with gantenerumab. Severity of AD-related amyloid neuropathology (lower CSF Aβ42) and comorbid cerebrovascular pathology (Fazekas score, total SS, and total microhemorrhage counts) may be important baseline ARIA-E risk factors, in addition to APOE ε4 allele count, and, in part, may increase risk because of higher baseline CAA burden. Symptomatic ARIA-E events tended to be radiologically more severe and were more frequently associated with ARIA-H vs asymptomatic cases. Although APOE ε4 allele count is associated with increased ARIA-E risk and increased radiological severity, it did not appear to influence symptomatic status among those who developed ARIA-E. In most participants, ARIA-E did not have a long-term impact on cognitive and functional performance.

These findings may be considered in clinical practice when prescribing anti-Aβ mAbs for early AD and developing individualized safety monitoring plans. Further evaluation of the identified potential ARIA-E risk factors in the context of other anti-Aβ mAbs is recommended.

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