Supplemental Online Content

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This supplemental material has been provided by the authors to give readers additional information about their work.

Supplementary Methods: Analysis for Risk Factors of Amyloid-Related Imaging Abnormalities – Edema (ARIA-E) in GRADUATE I and II

List of All Baseline Variables Evaluated

- Demographic: age, sex, race, ethnicity, region, Alzheimer's disease (AD) stage (prodromal versus mild)
- Genetic: apolipoprotein E (APOE) ε4 allele count (0, 1, 2)
- Study protocol number
- Clinical scales: Alzheimer's Disease Assessment Scale – Cognitive Subscale 13 (ADAS-Cog13), Mini-Mental State Examination (MMSE), Clinical Dementia Rating – Sum of Boxes (CDR-SB), Clinical Dementia Rating – Global Score (CDR-GS)
- Medical history and concomitant medications at baseline: the use of AD medications, cardiovascular risk factors (dyslipidemia, hypertension, diabetes; the presence of any cardiovascular risk factor[s]), antiplatelet agents (the use of antiplatelet therapy that is not acute acetylsalicylic acid or dosed as needed)
- Vital signs: weight, body mass index (BMI), systolic and diastolic blood pressure, pulse pressure
- Radiological: microhemorrhages and/or superficial siderosis (SS) (presence or absence, baseline total, baseline microhemorrhages, baseline SS), Fazekas score, lacunar infarcts (presence or absence)
- Volumetric magnetic resonance imaging (MRI): gray matter, whole brain, hippocampus
- Cerebrospinal (CSF) biomarker concentrations (log2 transformed [LT]):

    - AD core biomarkers: amyloid-beta ($A\beta_{42}$), total tau (tTau), phosphorylated tau (pTau)181, $A\beta_{40}$
    - NeuroToolKit: alpha-synuclein (α-syn), soluble triggering receptor expressed on myeloid cells 2 (sTREM2), neurofilament light chain (NfL), neurogranin, chitinase 3-like protein 1 (YKL 40), glial fibrillary acidic protein (GFAP), S100 calcium-binding protein B (S100B)
- Amyloid positron emission tomography (PET): composite region with whole cerebellum reference (centiloid [CL])
- Plasma biomarker concentrations (LT): $A\beta_{42}$, $A\beta_{40}$, pTau181, pTau217, GFAP, neuronal pentraxin-2 (NPTX2), growth differentiation factor-15 (GDF-15), NfL
- Laboratory values (log2 transformed): vitamin B12, methylmalonic acid (MMA), folic acid, glycosylated hemoglobin A1c (HbA1c), homocysteine

Further Details on Analysis

Each variable was tested in a univariate logistic regression model. Results include *P* values resulting from Bonferroni multiple testing corrections. Variables with a *P* value of < .05 in univariate modeling (without adjustment for multiple testing) were included in a backward stepwise multivariate logistic regression analysis to identify a reduced set of variables with an optimal model fit determined by Akaike information criterion.[2] To avoid model overfitting and a lack of convergence, and to maximize the possibility of identifying pertinent risk factors, this was repeated on three different combinations of the baseline variable groups (clinical + MRI + plasma; clinical + MRI + plasma + CSF; clinical + MRI + plasma + PET). In addition, univariate proportional hazards modeling was performed using the same variables. For continuous variables,

the odds ratio/hazard ratio is associated with a 1-point increase in the variable. For log-transformed variables, the odds ratio/hazard ratio is associated with a fold change.

eTable 1. GRADUATE I and II: Baseline Characteristics of Pooled Safety-evaluable MRI Population

	Placebo (n = 946)	Gantenerumab (n = 993)	Total (N = 1939)
Age, years			
N	946	993	1939
Mean (SD)	72.0 (7.6)	71.3 (7.8)	71.7 (7.7)
Median (range)	72.5 (51-89)	72.0 (50-90)	72.0 (50-90)
Age group, year, n (%)			
N	946	993	1939
< 65	168 (17.8)	185 (18.6)	353 (18.2)
≥ 65	778 (82.2)	808 (81.4)	1586 (81.8)
Sex, n (%)			
N	946	993	1939
Male	416 (44.0)	418 (42.1)	834 (43.0)
Female	530 (56.0)	575 (57.9)	1105 (57.0)
Ethnicity, n (%)[a]			
n	946	993	1939
Hispanic or Latino	171 (18.1)	161 (16.2)	332 (17.1)
Not Hispanic or Latino	770 (81.4)	824 (83.0)	1594 (82.2)
Not stated	2 (0.2)	5 (0.5)	7 (0.4)
Unknown	3(0.3)	3 (0.3)	6 (0.3)
Race, n (%)[a]			
n	946	993	1939
American Indian or Alaska Native	31 (3.3)	30 (3.0)	61 (3.1)
Asian	128 (13.5)	105 (10.6)	233 (12.0)
Black or African American	9 (1.0)	6 (0.6)	15 (0.8)

White	768 (81.2)	838 (84.4)	1606 (82.8)
Unknown[b]	10 (1.1)	14 (1.4)	24 (1.2)
Weight at baseline, kg			
n	946	993	1939
Mean (SD)	68.28 (13.80)	69.42 (14.67)	68.86 (14.26)
Median (range)	67.10 (37.5-119.1)	68.0 (36.3-133.8)	67.80 (36.3-133.8)
BMI at baseline, kg/m^2			
n	936	986	1922
Mean (SD)	25.21 (4.51)	25.51 (4.26)	25.36 (4.38)
Median (range)	24.64 (15.6-78.7)	25.12 (15.6-42.3)	24.96 (15.6-78.7)
Stratification region, no. (%)			
n	946	993	1939
Western Europe and Australia	375 (39.6)	399 (40.2)	774 (39.9)
North America	236 (24.9)	260 (26.2)	496 (25.6)
Others	335 (35.4)	334 (33.6)	669 (34.5)
APOE carrier status, no. (%)			
n	946	993	1939
Carrier	636 (67.2)	658 (66.3)	1294 (66.7)
Non-carrier	310 (32.8)	335 (33.7)	645 (33.3)
APOE allele, n (%)			
n	946	993	1939
0 APOE ε4 (non-carrier)	310 (32.8)	335 (33.7)	645 (33.3)
1 APOE ε4 (heterozygous carrier)	486 (51.4)	478 (48.1)	964 (49.7)
2 APOE ε4 (homozygous carrier)	150 (15.9)	180 (18.1)	330 (17.0)

	Placebo (n = 946)	Gantenerumab (n = 993)	Total (N = 1939)
Number of years of education			
n	946	993	1939
Mean (SD)	13.4 (4.1)	13.3 (4.0)	13.4 (4.0)
Median (range)	13.0 (1-27)	13.0 (3-26)	13.0 (1-27)
AD diagnosis at baseline, n (%)			
n	946	993	1939
Mild	426 (45.0)	451 (45.4)	877 (45.2)
Prodromal	520 (55.0)	542 (54.6)	1062 (54.8)
CDR-SB			
n	946	992	1938
Mean (SD)	3.61 (1.55)	3.68 (1.64)	3.64 (1.60)
Median (range)	3.50 (0.5-11.0)	3.5 (0.5-10.0)	3.5 (0.5-11.0)
CDR-GS, n (%)			
n	946	992	1938
0.5	710 (75.1)	688 (69.4)	1398 (72.1)
1	232 (24.5)	295 (29.7)	527 (27.2)
2	4 (0.4)	9 (0.9)	13 (0.7)
MMSE total score			
n	946	992	1938
Mean (SD)	23.7 (3.1)	23.6 (3.2)	23.6 (3.1)
Median (range)	24.0 (13-30)	24.0 (10-30)	24.0 (10-30)
ADAS-Cog13 total score			
n	939	984	1923
Mean (SD)	28.1 (6.9)	28.1 (7.0)	28.1 (6.9)
Median (range)	28.0 (9-62)	28.0 (6-58)	28.0 (6-62)

ADAS-Cog11 total score			
n	940	985	1925
Mean (SD)	17.1 (5.4)	17.2 (5.5)	17.1 (5.4)
Median (range)	17.0 (4–47)	17.0 (4–43)	17.0 (4–47)
ADCS-ADL total score			
n	938	989	1927
Mean (SD)	68.6 (6.9)	68.1 (7.2)	68.4 (7.1)
Median (range)	70.0 (36-78)	70.0 (31-78)	70.0 (31-78)
ADCS-ADL iADL score			
n	938	989	1927
Mean (SD)	49.9 (6.6)	49.4 (6.9)	49.6 (6.8)
Median (range)	52 (21-59)	51.0 (14-59)	51.0 (14-59)
ADCS-ADL bADL score			
n	938	989	1927
Mean (SD)	18.8 (0.7)	18.7 (0.8)	18.7 (0.7)
Median (range)	19.0 (12-19)	19.0 (12-19)	19.0 (12-19)
FAQ total score			
n	939	990	1929
Mean (SD)	7.3 (5.5)	7.8 (5.8)	7.6 (5.7)
Median (range)	6.0 (0-28)	7.0 (0-28)	7.0 (0-28)

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	Placebo (n = 946)	Gantenerumab (n = 993)	Total (N = 1939)
FCSRT free recall			
n	943	991	1934
Mean (SD)	8.6 (5.5)	9.0 (5.6)	8.8 (5.5)
Median (range)	8.0 (0–28)	8.0 (0–27)	8.0 (0–28)
FCSRT cueing index			
n	943	991	1934
Mean (SD)	0.426 (0.147)	0.435 (0.144)	0.431 (0.145)
Median (range)	0.442 (0-0.80)	0.444 (0-0.69)	0.442 (0-0.80)
AD medications present at baseline, n (%)			
n	946	993	1939
No	347 (36.7)	352 (35.4)	699 (36.0)
Yes	599 (63.3)	641 (64.6)	1240 (64.0)
Microhemorrhages and/or superficial siderosis present at baseline, n (%)			
n	946	993	1939
Absent	835 (88.3)	896 (90.2)	1731 (89.3)
Present	111 (11.7)	97 (9.8)	208 (10.7)
Baseline finding of microhemorrhages and/or superficial siderosis			
Baseline microhemorrhages and/or superficial siderosis, n (%)			
n	945	993	NA
0	834 (88.3)	896 (90.2)	NA
1–5	111 (11.7)	96 (9.7)	NA
> 5	0	1 (0.1)	NA
n, > 0 (%)	111 (11.7)	97 (9.8)	NA

Mean (SD)	1.4 (0.9)	1.8 (1.2)	NA
Median (range)	1.0 (1-5)	1.0 (1-6)	NA
Q1-Q3	1.0-1.0	1.0-2.0	NA
Baseline superficial siderosis, n (%)			
n	945	993	NA
0	924 (97.8)	967 (97.4)	
1–3	20 (2.1)	25 (2.5)	NA
> 3	1 (0.1)	1 (0.1)	NA
n, > 0 (%)	21 (2.2)	26 (2.6)	NA
Mean (SD)	1.3 (0.7)	1.7 (0.9)	NA
Median (range)	1.0 (1-4)	1.0 (1-5)	NA
Q1-Q3	1.0-1.0	1.0-2.0	NA
Baseline microhemorrhages, n (%)			
n	945	993	NA
0	845 (89.4)	913 (91.9)	NA
1–5	100 (10.6)	80 (8.1)	NA
> 5	0	0	NA
n, > 0 (%)	100 (10.6)	80 (8.1)	NA
Mean (SD)	1.3 (0.7)	1.6 (1.0)	NA
Median (range)	1.0 (1-5)	1.0 (1-5)	NA
Q1-Q3	1.0-1.0	1.0-2.0	NA

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105 Abbreviations: AD, Alzheimer disease; ADAS-Cog11, Alzheimer Disease

106 Assessment Scale, Cognition Subscale 11; ADAS-Cog13, Alzheimer Disease

107 Assessment Scale, Cognition Subscale 13; ADCS-ADL, Alzheimer Disease

108 Cooperative Study Group Activities of Daily Living; APOE, apolipoprotein E; BMI,

Body Mass Index; CDR, Clinical Dementia Rating – Global Score; CDR, Clinical Dementia Rating – Sum of Boxes; FAQ, Functional Activities Questionnaire; FCSRT, Free and Cued Selective Reminding Test; MMSE, Mini-Mental State Examination; MRI, magnetic resonance imaging; Q, quartile; SD, standard deviation.

[a] Self-declared race and ethnicity were collected for the purpose of pre-specified subgroup analyses.

[b] Reported as unknown if not allowed to be collected based on local regulation.

117 **eTable 2. PostGraduate: Demographic and Baseline Characteristics**

Characteristics	Previous Treatment: Placebo (n = 705)	Previous Treatment: Gantenerumab (n = 676)
Sex, n (%)		
Female	394 (55.9)	400 (59.2)
Male	311 (44.1)	276 (40.8)
Age, mean (SD), y	73.7 (7.5)	73.0 (7.7)
Weight, mean (SD), kg	68.1 (13.8)	68.8 (13.8)
BMI, mean (SD), kg/m^2	25.2 (4.2)	25.5 (4.4)
Race, n (%)[a]		
American Indian or Alaska Native	25 (3.5)	22 (3.3)
Asian	105 (14.9)	88 (13.0)
Black or African American	6 (0.9)	4 (0.6)
White	557 (79.0)	546 (80.8)
Unknown[b]	12 (1.7)	16 (2.4)
Ethnicity, n. (%)[a]		
Hispanic or Latino	120 (17.0)	105 (15.5)
Not Hispanic or Latino	581 (82.4)	566 (83.7)
Not stated	1 (0.1)	3 (0.4)
Unknown	3 (0.4)	2 (0.3)
Education, mean (SD), y	13.6 (4.2)	13.2 (4.0)
APOE carrier, n (%)		
Carrier	488 (69.2)	452 (66.9)
Non-carrier	217 (30.8)	224 (33.1)
APOE allele, n (%)		
0 APOE ε4 (non-carrier)	217 (30.8%)	224 (33.1%)

1 APOE ε4 (heterozygous carrier)	373 (52.9%)	344 (50.9%)
2 APOE ε4 (homozygous carrier)	115 (16.3%)	108 (16.0%)

Abbreviations: APOE, apolipoprotein E; BMI, body mass index; OLE, open-label extension; SD, standard deviation.

Baseline (OLE study day 1) was considered the first dosing visit in the OLE (first dosing in PostGraduate study or first dosing in the OLE period of the parent GRADUATE studies). The number shown included all the participants who completed the up-titration either in the parent GRADUATE study or in the PostGraduate study.

[a] Self-declared race and ethnicity were collected for the purpose of pre-specified subgroup analyses.

[b] Reported as unknown if not allowed to be collected based on local regulation.

eTable 3. Analysis for Risk Factors of ARIA-E in GRADUATE I and II, Demographic and Baseline Characteristics of Participants

	No ARIA-E (n = 746)	ARIA-E (n = 247)	Total (N = 993)
Study, n (%)			
n	746	247	993
GRADUATE I	378 (50.7)	119 (48.2)	497 (50.1)
GRADUATE II	368 (49.3)	128 (51.8)	496 (49.9)
Sex, n (%)			
n	746	247	993
Female	415 (55.6)	160 (64.8)	575 (57.9)
Male	331 (44.4)	87 (35.2)	418 (42.1)
Race, n (%)[a]			
n	746	247	993
White	628 (84.2)	210 (85.0)	838 (84.4)
American Indian or Alaska Native	22 (2.9)	8 (3.2)	30 (3.0)
Asian	80 (10.7)	25 (10.1)	105 (10.6)
Black or African American	4 (0.5)	2 (0.8)	6 (0.6)
Unknown[b]	12 (1.6)	2 (0.8)	14 (1.4)
Ethnicity, n (%)[a]			
n	746	247	993
Not Hispanic or Latino	618 (82.8)	206 (83.4)	824 (83.0)
Hispanic or Latino	122 (16.4)	39 (15.8)	161 (16.2)
Not reported	3 (0.4)	2 (0.8)	5 (0.5)
Unknown	3 (0.4)	0	3 (0.3)
Geographic region, n (%)			
n	746	247	993

Western Europe and Australia	342 (45.8)	108 (43.7)	450 (45.3)
North America	187 (25.1)	73 (29.6)	260 (26.2)
Others	217 (29.1)	66 (26.7)	283 (28.5)
Age, years			
n	746	247	993
Mean (SD)	71.44 (8.13)	70.98 (6.90)	71.33 (7.84)
Median (range)	72 (50–90)	71 (51–88)	72 (50–90)
AD disease stage, n (%)			
n	746	247	993
Mild	343 (46.0)	108 (43.7)	451 (45.4)
Prodromal	403 (54.0)	139 (56.3)	542 (54.6)
Use of symptomatic AD medication, n (%)			
n	746	247	993
No	265 (35.5)	87 (35.2)	352 (35.4)
Yes	481 (64.5)	160 (64.8)	641 (64.6)
Number of APOE ε4 alleles, n (%)			
n	746	247	993
0 APOE ε4 (non-carrier)	291 (39.0)	44 (17.8)	335 (33.7)
1 APOE ε4 (heterozygous carrier)	361 (48.4)	117 (47.4)	478 (48.1)
2 APOE ε4 (homozygous carrier)	94 (12.6)	86 (34.8)	180 (18.1)
Presence of microhemorrhages and/or superficial siderosis			
n	746	247	993
Absent	677 (90.8)	219 (88.7)	896 (90.2)
Present	69 (9.2)	28 (11.3)	97 (9.8)

	No ARIA-E (n = 746)	ARIA-E (n = 247)	Total (N = 993)
Weight, kg			
n	746	247	993
Mean (SD)	69.98 (14.69)	67.73 (14.49)	69.42 (14.67)
Median (range)	68.9 (36.3–130.2)	67.0 (39.1–133.8)	68.0 (36.3–133.8)
BMI, kg/m^2			
n	743	243	986
Mean (SD)	25.65 (4.32)	25.11 (4.05)	25.51 (4.26)
Median (range)	25.2 (15.61–42.31)	25.0 (16.16–41.14)	25.1 (15.61–42.31)
CDR-SB score			
n	745	247	992
Mean (SD)	3.69 (1.63)	3.66 (1.69)	3.68 (1.64)
Median (range)	3.5 (0.5–10)	3.5 (0.5–10)	3.5 (0.5–10)
CDR-GS, n (%)			
n	745	247	992
0.5	516 (69.3)	172 (69.6)	688 (69.4)
1	222 (29.8)	73 (29.6)	295 (29.7)
2	7 (0.9)	2 (0.8)	9 (0.9)
MMSE			
n	745	247	992
Mean (SD)	23.63 (3.11)	23.50 (3.30)	23.59 (3.16)
Median (range)	24 (13–30)	24 (10–30)	24 (10–30)
ADAS-Cog13			
n	738	246	984
Mean (SD)	28.00 (7.11)	28.48 (6.50)	28.12 (6.97)
Median (range)	28 (6–54)	28 (10–58)	28 (6–58)

Diastolic blood pressure, mmHg			
n	746	247	993
Mean (SD)	75.78 (8.89)	76.60 (9.12)	75.98 (8.95)
Median (range)	76 (51–102)	77 (54–110)	76 (51–110)
Systolic blood pressure, mmHg			
n	746	247	993
Mean (SD)	131.87 (15.05)	134.28 (15.85)	132.47 (15.28)
Median (range)	131 (90–195)	134 (95–185)	132 (90–195)
Pulse pressure, mmHg			
n	746	247	993
Mean (SD)	56.10 (13.31)	57.68 (14.18)	56.49 (13.54)
Median (range)	55 (20–105)	56 (20–103)	55 (20–105)
Total microhemorrhages and superficial siderosis			
n	746	247	993
Mean (SD)	0.15 (0.58)	0.25 (0.80)	0.17 (0.64)
Median (range)	0 (0–6)	0 (0–5)	0 (0–6)
Total microhemorrhages			
n	746	247	993
Mean (SD)	0.11 (0.46)	0.18 (0.70)	0.13 (0.53)
Median (range)	0 (0–5)	0 (0–5)	0 (0–5)
Total SS			
n	746	247	993
Mean (SD)	0.04 (0.29)	0.06 (0.33)	0.04 (0.30)
Median (range)	0 (0–5)	0 (0–3)	0 (0–5)

	No ARIA-E (n = 746)	ARIA-E (n = 247)	Total (N = 993)
Fazekas score			
n	746	247	993
Mean (SD)	0.69 (0.58)	0.85 (0.58)	0.73 (0.58)
Median (range)	1 (0–2)	1 (0–2)	1 (0–2)
CSF Aβ42, LT			
n	222	67	289
Mean (SD)	9.13 (0.45)	8.89 (0.5)	9.07 (0.47)
Median (range)	9.2 (7.96–10.47)	8.8 (7.48–9.87)	9.1 (7.48–10.47)
CSF total tau, LT			
n	222	67	289
Mean (SD)	8.14 (0.53)	8.3 (0.61)	8.18 (0.56)
Median (range)	8.2 (6.58–9.68)	8.3 (6.68–9.68)	8.2 (6.58–9.68)
CSF phosphorylated tau, LT			
n	222	67	289
Mean (SD)	4.82 (0.58)	5.03 (0.65)	4.87 (0.6)
Median (range)	4.9 (3.19–6.57)	5.1 (3.12–6.5)	4.9 (3.12–6.57)
CSF Aβ40, LT			
n	217	66	283
Mean (SD)	13.91 (0.5)	13.9 (0.5)	13.91 (0.5)
Median (range)	13.9 (12.42–15.03)	13.9 (12.2–15.05)	13.9 (12.2–15.05)
CSF α-synuclein, LT			
n	216	67	283
Mean (SD)	7.99 (0.78)	8.08 (0.71)	8.01 (0.77)
Median (range)	7.9 (5.98–11.18)	8.1 (6.47–10.95)	7.9 (5.98–11.18)

CSF sTREM2, LT			
n	218	67	285
Mean (SD)	3.45 (0.58)	3.53 (0.49)	3.47 (0.56)
Median (range)	3.5 (-0.82–4.56)	3.5 (2.32–4.61)	3.5 (-0.82–4.61)
CSF NfL, LT			
n	219	67	286
Mean (SD)	7.44 (0.69)	7.46 (0.6)	7.44 (0.67)
Median (range)	7.4 (5.67–10.46)	7.5 (5.96–9.08)	7.4 (5.67–10.46)
CSF neurogranin, LT			
n	218	67	285
Mean (SD)	10.25 (0.55)	10.35 (0.62)	10.28 (0.57)
Median (range)	10.3 (8.63–12.26)	10.4 (8.47–12.08)	10.3 (8.47–12.26)
CSF YKL-40 glycoprotein, LT			
n	219	67	286
Mean (SD)	17.7 (0.58)	17.8 (0.49)	17.72 (0.56)
Median (range)	17.7 (16.09–19.26)	17.8 (16.3–19.07)	17.7 (16.09–19.26)
CSF GFAP, LT			
n	219	67	286
Mean (SD)	13.46 (0.66)	13.46 (0.59)	13.46 (0.64)
Median (range)	13.4 (11.95–17.21)	13.6 (12.1–14.98)	13.4 (11.95–17.21)
CSF S100			
n	217	67	284
Mean (SD)	-0.26 (0.48)	-0.24 (0.44)	-0.26 (0.47)
Median (range)	-0.3 (-1.78–1.82)	-0.3 (-1.11–0.98)	-0.3 (-1.78–1.82)

	No ARIA-E (n = 746)	ARIA-E (n = 247)	Total (N = 993)
Plasma Aβ40, LT			
n	743	246	989
Mean (SD)	4.9 (0.35)	4.89 (0.34)	4.9 (0.35)
Median (range)	4.9 (1.83–6.61)	4.9 (2.75–6.79)	4.9 (1.83–6.79)
Plasma phosphorylated tau 181, LT			
n	743	246	989
Mean (SD)	0.56 (0.54)	0.57 (0.49)	0.56 (0.53)
Median (range)	0.6 (-1.91–2.68)	0.6 (-0.85–2.52)	0.6 (-1.91–2.68)
Plasma GDF 15, LT			
n	687	229	916
Mean (SD)	10.26 (0.61)	10.18 (0.56)	10.24 (0.6)
Median (range)	10.2 (8.84–12.46)	10.2 (8.9–12.08)	10.2 (8.84–12.46)
Plasma homocysteine, LT			
n	742	246	988
Mean (SD)	3.82 (0.38)	3.81 (0.4)	3.82 (0.38)
Median (range)	3.8 (2.46–5.21)	3.8 (2.94–5.03)	3.8 (2.46–5.21)
Plasma NfL, LT			
n	737	244	981
Mean (SD)	1.99 (0.63)	1.94 (0.54)	1.98 (0.61)
Median (range)	2 (-0.87–4.88)	1.9 (0.24–3.71)	2 (-0.87–4.88)
Plasma Aβ40, LT			
n	743	246	989
Mean (SD)	8.17 (0.32)	8.15 (0.29)	8.16 (0.31)
Median (range)	8.2 (4.58–9.9)	8.2 (6.38–9.89)	8.2 (4.58–9.9)

Plasma phosphorylated 217 tau, LT			
n	541	173	714
Mean (SD)	-0.95 (0.67)	-0.92 (0.53)	-0.94 (0.64)
Median (range)	-0.9 (-3.8–1.01)	-1 (2.16–0.95)	-0.9 (-3.8–1.01)
Plasma GFAP, LT			
n	739	246	985
Mean (SD)	7.25 (0.62)	7.3 (0.6)	7.26 (0.62)
Median (range)	7.3 (5.07–9.79)	7.2 (5.69–11.23)	7.3 (5.07–11.23)
Amyloid PET, CL			
n	448	162	610
Mean (SD)	91.93 (28.44)	97.61 (29.89)	93.44 (28.91)
Median (range)	92.4 (5.30–175.67)	96.6 (12.15–201.92)	93.4 (5.30–201.92)
Volumetric MRI, cortical grey matter			
n	743	247	990
Mean (SD)	517.44 (36.18)	523.77 (35.45)	519.02 (36.08)
Median (range)	518.8 (380.80–622.03)	522.4 (420.56–635.89)	519.8 (380.80–635.89)
Volumetric MRI, whole brain			
n	745	247	992
Mean (SD)	1309.02 (64.56)	1323.65 (66.30)	1312.67 (65.27)
Median (range)	1307.7 (1113.67–1525.80)	1319.2 (1114.89–1572.85)	1311.1 (1113.67–1572.85)

	No ARIA-E (n = 746)	ARIA-E (n = 247)	Total (N = 993)
Volumetric MRI, total hippocampus			
n	745	247	992
Mean (SD)	6.32 (1.12)	6.05 (1.04)	6.25 (1.11)
Median (range)	6.3 (2.80–9.75)	6.0 (3.14–8.56)	6.2 (2.80–9.75)
Presence of lacunar infarcts, n (%)			
n	746	247	993
No	728 (97.6)	240 (97.2)	968 (97.5)
Yes	18 (2.4)	7 (2.8)	25 (2.5)
Diabetes, n (%)			
n	746	247	993
No	635 (85.1)	223 (90.3)	858 (86.4)
Yes	111 (14.9)	24 (9.7)	135 (13.6)
Dyslipidemia, n (%)			
n	746	247	993
No	124 (16.6)	24 (9.7)	148 (14.9)
Yes	622 (83.4)	223 (90.3)	845 (85.1)
Hypertension, n (%)			
n	746	247	993
No	381 (51.1)	135 (54.7)	516 (52.0)
Yes	365 (48.9)	112 (45.3)	477 (48.0)
Any cardiovascular risk flag, n (%)			
n	746	247	993
No	52 (7.0)	18 (7.3)	70 (7.0)
Yes	694 (93.0)	229 (92.7)	923 (93.0)

Vitamin B12, LT			
n	746	246	992
Mean (SD)	8.29 (1.01)	8.28 (0.83)	8.29 (0.97)
Median (range)	8.1 (6.79–14.55)	8.1 (6.92–12.83)	8.1 (6.79–14.55)
Methylmalonic acid, LT			
n	744	247	991
Mean (SD)	7.4 (0.58)	7.42 (0.52)	7.4 (0.57)
Median (range)	7.4 (4.64–9.86)	7.4 (6.07–8.71)	7.4 (4.64–9.86)
Folic acid, LT			
n	746	246	992
Mean (SD)	5.2 (1.19)	5.14 (1.22)	5.18 (1.2)
Median (range)	5 (2.96–9.81)	4.9 (3.2–9.81)	5 (2.96–9.81)
Hemoglobin A1c, LT			
n	743	246	989
Mean (SD)	5.26 (0.19)	5.25 (0.17)	5.26 (0.19)
Median (range)	5.2 (4.74–6)	5.2 (4.62–5.84)	5.2 (4.62–6)
Antiplatelet therapy, n (%)			
n	746	247	993
No	562 (75.3)	188 (76.1)	750 (75.5)
Yes	184 (24.7)	59 (23.9)	243 (24.5)
CSF NPTX2, LT			
n	218	67	285
Mean (SD)	12.18 (0.7)	12.24 (0.68)	12.2 (0.69)
Median (range)	12.2 (10.48–13.74)	12.2 (10.76–13.79)	12.2 (10.48–13.79)

Abbreviations: AD, Alzheimer disease; ADAS-Cog13, Alzheimer Disease Assessment Scale, Cognition Subscale 13; APOE, apolipoprotein E; ARIA-E,

amyloid-related imaging abnormalities-edema; BMI, Body Mass Index; CDR, Clinical Dementia Rating; CDR-GS, Clinical Dementia Rating-global score; CDR-SB, Clinical Dementia Rating-Sum of Boxes; CSF, cerebrospinal fluid; GDF-15, growth differentiation factor 15; GFAP, glial fibrillary acidic protein; LT, Log 2 transformed; MMSE, mini mental state examination; MRI, magnetic resonance imaging; NPTX2, neuronal pentraxin 2; PET, positron emission tomography; SD, standard deviation; SS, superficial siderosis; sTREM2, soluble triggering receptor expressed on myeloid cells 2.

All the variables as measured at baseline unless indicated otherwise.

[a] Self-declared race and ethnicity were collected for the purpose of pre-specified subgroup analyses.

[b] Reported as unknown if not allowed to be collected based on local regulation.

eTable 4. Risk Factors for ARIA-E With Concurrent ARIA-H: Multivariate Modeling With Stepwise Logistic Regression for Baseline Variables With Univariate *P* <.05

Variable	Odds Ratio [95% CI]
***Clinical variables and plasma biomarkers* model**	
APOE ε4 homozygous carrier	6.276 [3.505–11.237]
Fazekas score at screening	2.206 [1.559–3.123]
APOE ε4 heterozygous carrier	2.079 [1.209–3.575]
Total microhemorrhages and SS at screening	1.452 [1.151–1.83]
Volumetric MRI – cortical gray matter (mL)	1.007 [1.001–1.013]
Volumetric MRI – total hippocampus (mL)	0.791 [0.651–0.96]
***Clinical variables and plasma + CSF Biomarkers* model**	
APOE ε4 homozygous carrier	6.926 [2.01–23.866]
Fazekas score at screening	4.478 [1.872–10.713]
CSF phosphorylated tau (LT)	3.824 [1.837–7.958]
Total microhemorrhages and SS at screening	3.109 [0.92–10.511]
APOE ε4 heterozygous carrier	2.287 [0.75–6.972]
CSF $A\beta_{42}$ (LT)	0.163 [0.06–0.442]
Presence of microhemorrhages and/or SS at screening	0.125 [0.007–2.131]
***Clinical variables and plasma + amyloid PET biomarkers* model**	
APOE ε4 homozygous carrier	5.904 [2.734–12.747]
Fazekas score at screening	2.095 [1.36–3.227]
APOE ε4 heterozygous carrier	2.072 [1.02–4.21]
Total microhemorrhages and SS at screening	1.713 [1.285–2.285]
Amyloid PET (CL)	1.012 [1.004–1.021]
Volumetric MRI – cortical gray matter (mL)	1.008 [1.001–1.016]

Volumetric MRI – total hippocampus (mL)	0.761 [0.594–0.975]

Abbreviations: Aβ, amyloid-beta; APOE, apolipoprotein E; ARIA-E, amyloid-related imaging abnormalities – edema; CI, confidence interval; CSF, cerebrospinal fluid; LT, log2 transformed; MRI, magnetic resonance imaging; PET, positron emission tomography.

APOE ε4 and the presence of microhemorrhages and/or superficial siderosis are treated as categorical variables, with APOE 0ε4 and microhemorrhage and/or superficial siderosis absence as the reference levels.

All the variables as measured at baseline unless indicated otherwise.

169 **eTable 5. GRADUATE I and II: Nature and Severity of CNS Symptoms in Serious**

170 **Symptomatic ARIA-E Cases**

MedDRA SOC, MedDRA Preferred Term	Intensity	Placebo (n = 946)	Gantenerumab (n = 993)
Any event, no. (%)	Any	0	12 (1.2)
	Mild	0	1 (0.1)
	Moderate	0	4 (0.4)
	Severe	0	7 (0.7)
Nervous system disorders, n (%)			
Overall	Any	0	8 (0.8)
	Mild	0	1 (0.1)
	Moderate	0	2 (0.2)
	Severe	0	5 (0.5)
Aphasia	Any	0	3 (0.3)
	Mild	0	0
	Moderate	0	2 (0.2)
	Severe	0	1 (0.1)
Headache	Any	0	3 (0.3)
	Mild	0	1 (0.1)
	Moderate	0	2 (0.2)
	Severe	0	0
Encephalopathy	Any	0	2 (0.2)
	Mild	0	0
	Moderate	0	0
	Severe	0	2 (0.2)
Apraxia	Any	0	1 (0.1)
	Mild	0	0

	Moderate	0	1 (0.1)
	Severe	0	0
Dizziness	Any	0	1 (0.1)
	Mild	0	0
	Moderate	0	0
	Severe	0	1 (0.1)
Dysarthria	Any	0	1 (0.1)
	Mild	0	0
	Moderate	0	0
	Severe	0	1 (0.1)
Dyspraxia	Any	0	1 (0.1)
	Mild	0	0
	Moderate	0	1 (0.1)
	Severe	0	0
Focal dyscognitive seizures	Any	0	1 (0.1)
	Mild	0	0
	Moderate	0	0
	Severe	0	1 (0.1)
Hemianopia	Any	0	1 (0.1)
	Mild	0	0
	Moderate	0	0
	Severe	0	1 (0.1)

MedDRA System Organ Class, MedDRA Preferred Term	Intensity	Placebo (n = 946)	Gantenerumab (n = 993)
Hemiparesis	Any	0	1 (0.1)
	Mild	0	0
	Moderate	0	0
	Severe	0	1 (0.1)
Memory impairment	Any	0	1 (0.1)
	Mild	0	1 (0.1)
	Moderate	0	0
	Severe	0	0
Myoclonus	Any	0	1 (0.1)
	Mild	0	0
	Moderate	0	1 (0.1)
	Severe	0	0
Status epilepticus	Any	0	1 (0.1)
	Mild	0	0
	Moderate	0	1 (0.1)
	Severe	0	0
Psychiatric disorders, n (%)			
Overall	Any	0	5 (0.5)
	Mild	0	1 (0.1)
	Moderate	0	3 (0.3)
	Severe	0	1 (0.1)
Confusional state	Any	0	2 (0.2)
	Mild	0	1 (0.1)
	Moderate	0	1 (0.1)
	Severe	0	0

Mental status changes	Any	0	2 (0.2)
	Mild	0	0
	Moderate	0	1 (0.1)
	Severe	0	1 (0.1)
Abnormal behavior	Any	0	1 (0.1)
	Mild	0	0
	Moderate	0	1 (0.1)
	Severe	0	0
Hallucination, visual	Any	0	1 (0.1)
	Mild	0	0
	Moderate	0	1 (0.1)
	Severe	0	0
Psychomotor retardation	Any	0	1 (0.1)
	Mild	0	0
	Moderate	0	1 (0.1)
	Severe	0	0

MedDRA System Organ Class, MedDRA Preferred Term	Intensity	Placebo (n = 946)	Gantenerumab (n = 993)
Ear and labyrinth disorders, n (%)			
Overall	Any	0	1 (0.1)
	Mild	0	0
	Moderate	0	0
	Severe	0	1 (0.1)
Vestibular disorder	Any	0	1 (0.1)
	Mild	0	0
	Moderate	0	0
	Severe	0	1 (0.1)
Eye disorders, n (%)			
Overall	Any	0	1 (0.1)
	Mild	0	1 (0.1)
	Moderate	0	0
	Severe	0	0
Vision blurred	Any	0	1 (0.1)
	Mild	0	1 (0.1)
	Moderate	0	0
	Severe	0	0
General disorders and administration site conditions, n (%)			
Overall	Any	0	1 (0.1)
	Mild	0	1 (0.1)
	Moderate	0	0
	Severe	0	0
Gait disturbance	Any	0	1 (0.1)

	Mild	0	1 (0.1)
	Moderate	0	0
	Severe	0	0

Abbreviations: AE, adverse event; ARIA-E, amyloid-related imaging abnormalities-edema; CNS, central nervous system; MedDRA, Medical Dictionary for Regulatory Activities; MRI, magnetic resonance imaging; SOC, system organ class.

Investigator text for AEs is coded using MedDRA version 25.0.

All counts represent ARIA-E MRI findings with at least one associated CNS symptom. Multiple occurrences of the same associated CNS symptom with one ARIA-E MRI finding are counted once at the greatest intensity for this preferred term. To the SOC Overall row counts, an ARIA-E MRI finding contributes only with the associated CNS symptoms occurring with the greatest intensity within the SOC.

All CNS symptoms temporally associated with ARIA-E MRI findings are considered, and may therefore include some AEs occurring after the AE reporting period, which would not be reported in standard non-CNS AE outputs.

eTable 6. GRADUATE I and II: Summary of Changes in Clinical Symptomatology from First to Second ARIA-E Episode, Gantenerumab Arm

Symptomatic status of first ARIA-E episode	Symptomatic status of second ARIA-E episode		
	Asymptomatic	**Symptomatic**	**Total**
Asymptomatic	70	10	80
Symptomatic	12	3	15
Total	82	13	95

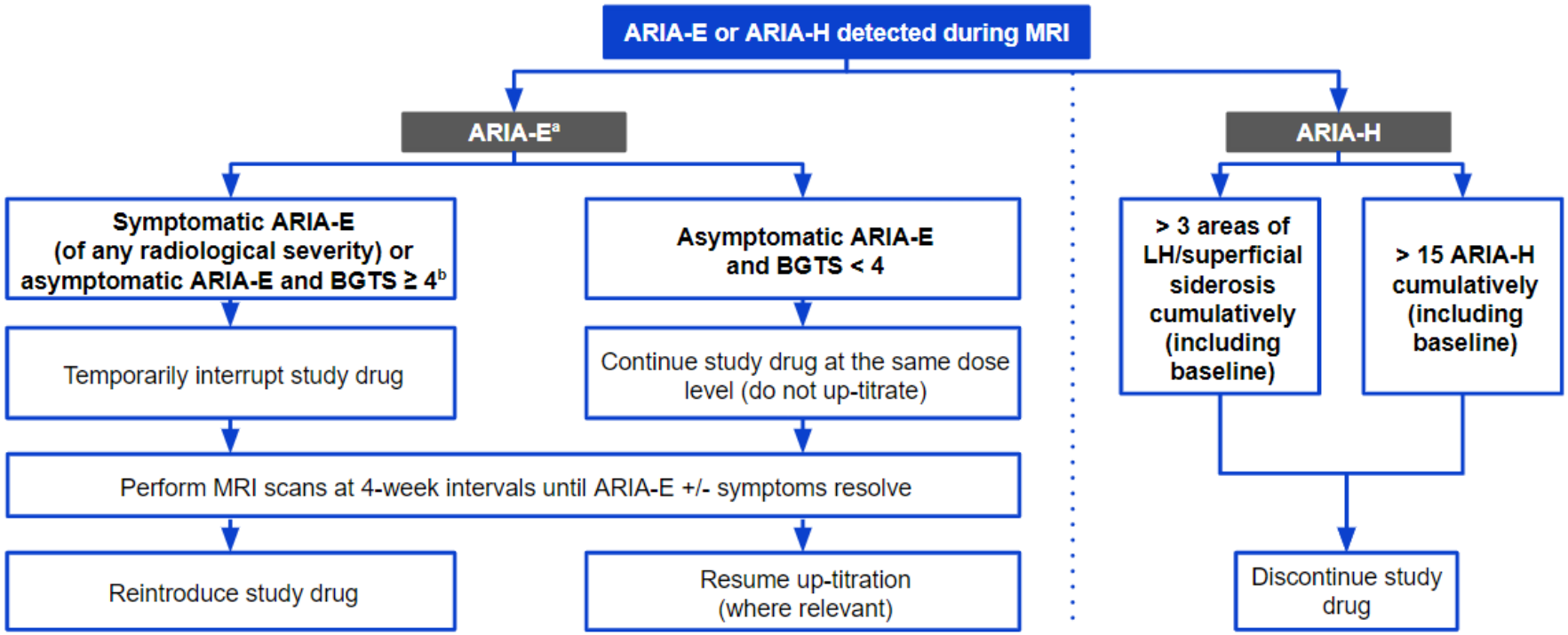
Abbreviations: ARIA-E, amyloid-related imaging abnormalities – edema.

eTable 7. GRADUATE I and II: Summary of Radiological Severity of ARIA-E MRI Findings by Concurrence with New ARIA-H MRI Findings

MRI findings by APOE genotype	Placebo (n = 946)	Gantenerumab (n = 993)
Radiological severity of all ARIA-E episodes with concurrent new ARIA-H (BGTS)		
n	7	178
Mean (SD)	4.1 (2.6)	11.9 (8.9)
Median	3.0	9.0
Radiological severity of all ARIA-E episodes without concurrent new ARIA-H (BGTS)		
n	22	202
Mean (SD)	3.5 (3.2)	6.4 (5.0)
Median	2.5	5.0

Abbreviations: APOE, apolipoprotein E; ARIA-E, amyloid-related imaging abnormalities – edema; ARIA-H, amyloid-related imaging abnormalities – hemosiderin BGTS, Barkhof Grand Total Scale; MRI, magnetic resonance imaging; SD, standard deviation.

eFigure 1. GRADUATE I and II: ARIA-Related Dosing Intervention Rules

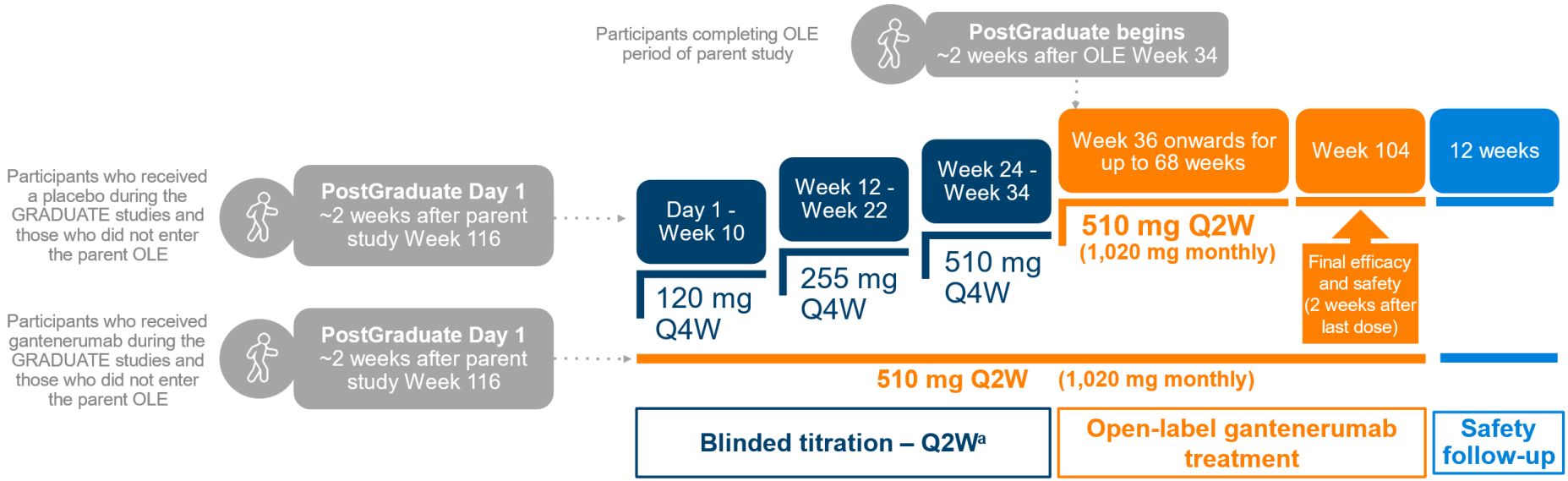


Abbreviations: AE, adverse event, ARIA-E, amyloid-related imaging abnormalities – edema; ARIA-H, amyloid-related imaging abnormalities – hemosiderin; BGTS, Barkhof Grand Total Scale; CNS, central nervous system; LH, leptomeningeal hemosiderosis; MRI, magnetic resonance imaging.

[a] Any recurrence of ARIA-E was treated the same as the first event.

[b] Symptomatic ARIA-E is defined as ARIA-E temporally associated with CNS symptoms. Symptomatic ARIA-E, ARIA that resulted in change in study treatment or ARIA otherwise clinically significant in the investigator's judgment were required to be reported as AE, per the protocol.

eFigure 2. PostGraduate: Study Design



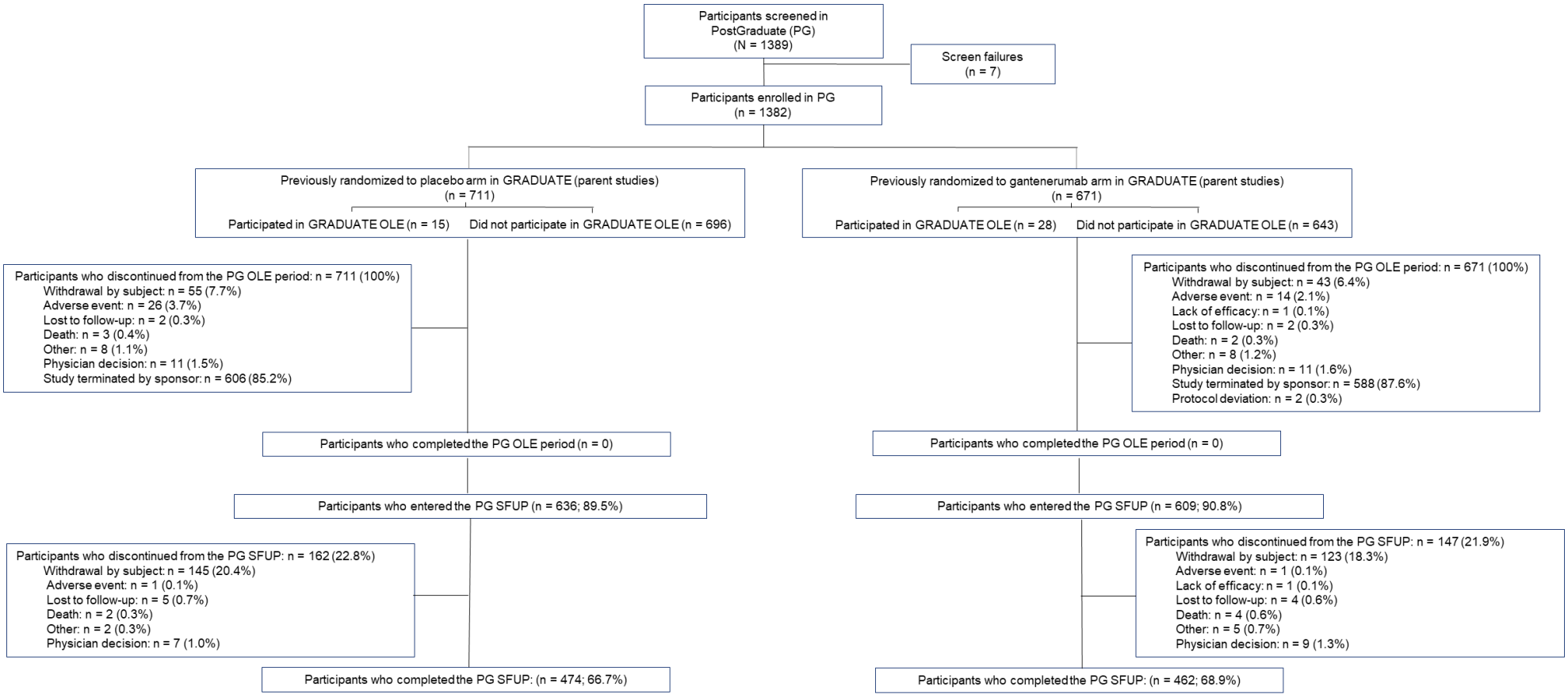
Abbreviations: OLE, open-label extension; Q2W, every 2 weeks; Q4W, every 4 weeks.

All participants had received Q2W injections during the uptitration to maintain the blind to the previous treatment allocation in the parent studies.

For a small subset of participants for whom POSTGRADUATE was not available at the time of completion of the double-blind period of the parent study, they entered an OLE period within the parent study. These participants joined the POSTGRADUATE study approximately 2 weeks after OLE week 34, once they completed uptitration.

[a] Participants who received gantenerumab during the double-blind period continued to receive gantenerumab 510 mg Q2W while undergoing a mock uptitration. Participants who received placebo during the double-blind period had undergone an uptitration with gantenerumab.

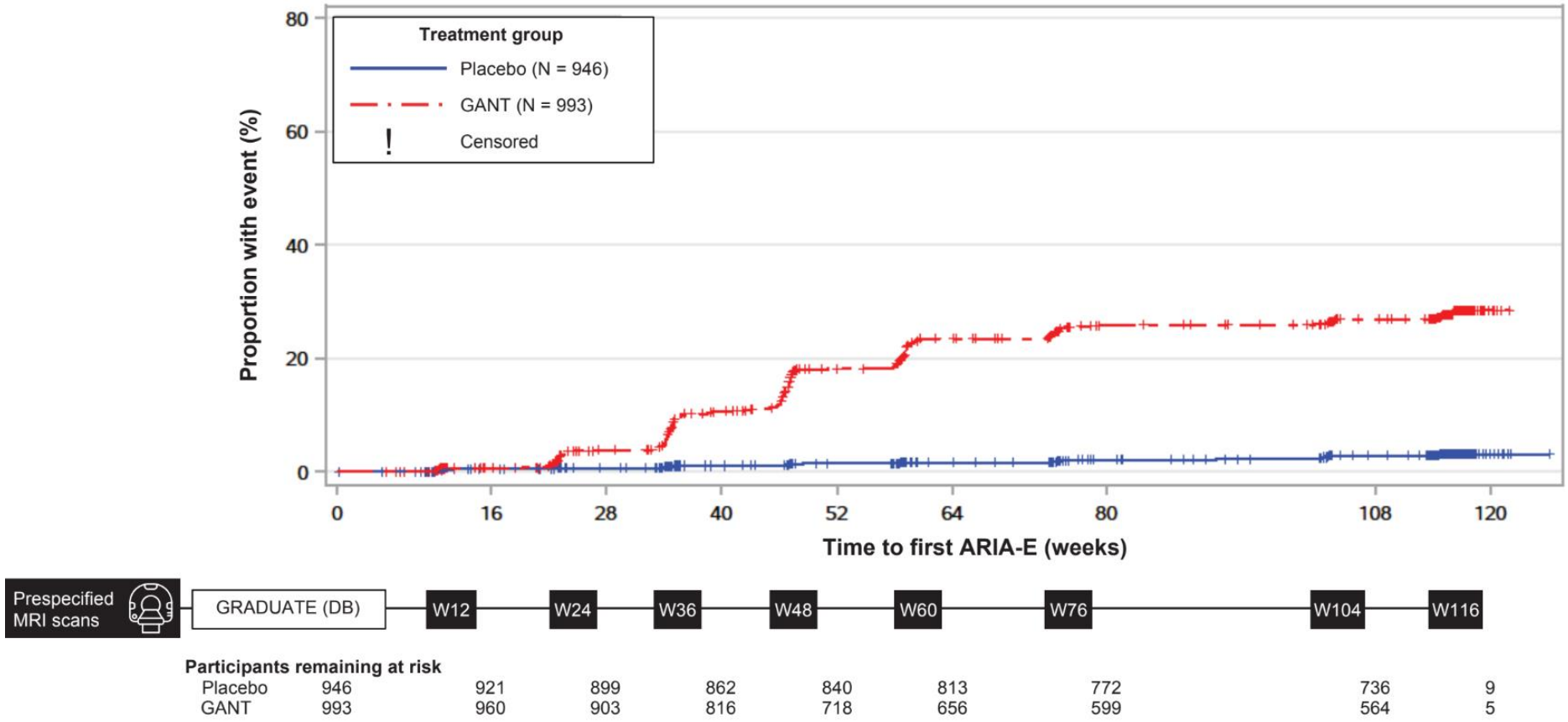
eFigure 3. PostGraduate: Participant Flow



Abbreviations: DB, double-blind; OLE, open-label extension; PG, PostGraduate; SFUP, Safety Follow-up Period.

Any participant who had completed GRADUATE I or GRADUATE II, either the DB or OLE part, as applicable, and did not discontinue study drug early was eligible for enrollment in this study if they met the inclusion/exclusion criteria. Participants were enrolled at 270 sites from February 1, 2021 and the PostGraduate study was terminated March 6, 2023 after the GRADUATE studies did not meet their primary endpoint.[1]

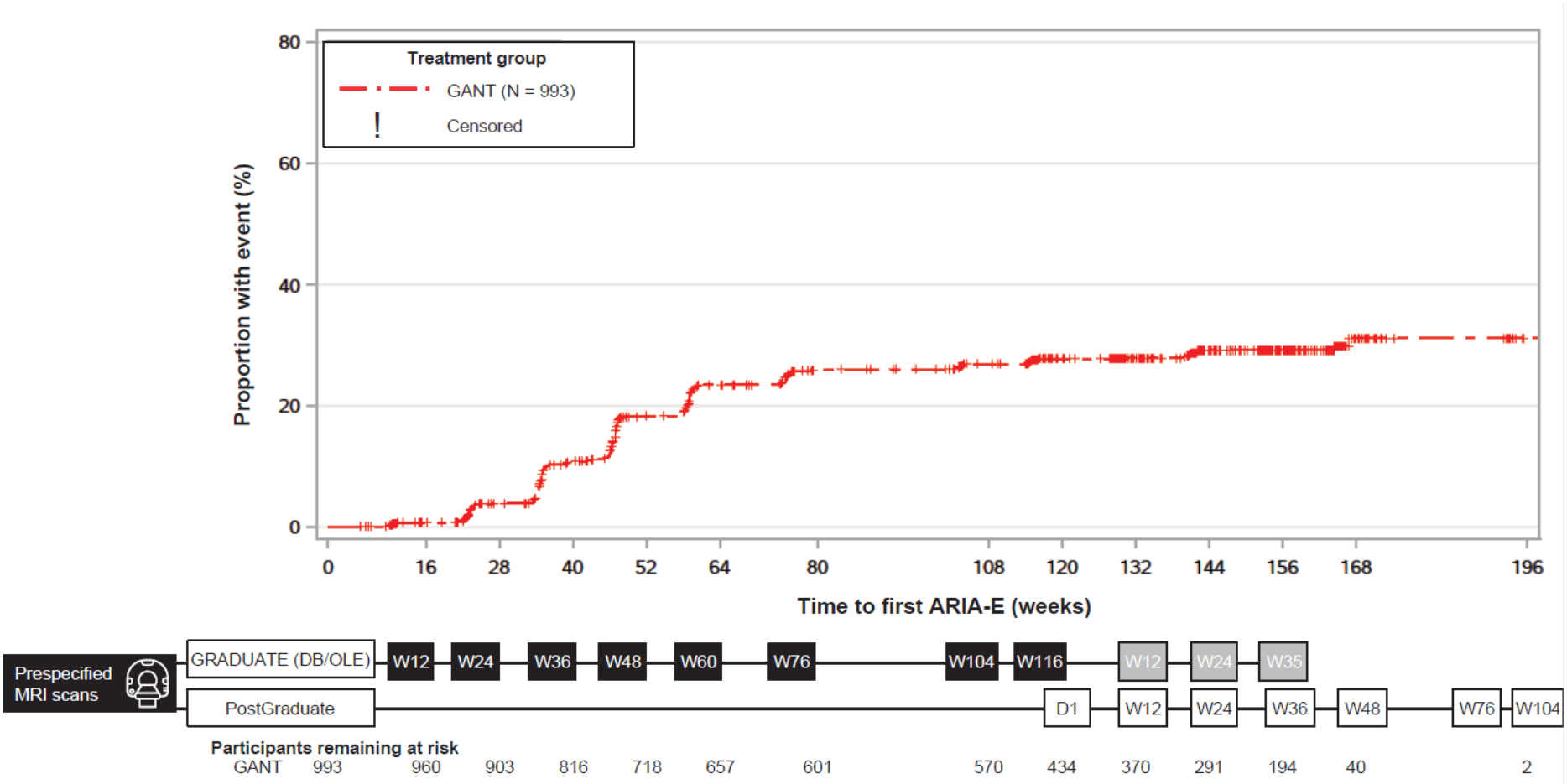
eFigure 4. Kaplan-Meier Plot of Time-to-Onset of First ARIA-E Event in the Double-Blind Period of GRADUATE Trials



Abbreviations: ARIA-E, amyloid-related imaging abnormalities-edema; DB, double-blind; GANT, gantenerumab; W, weeks.

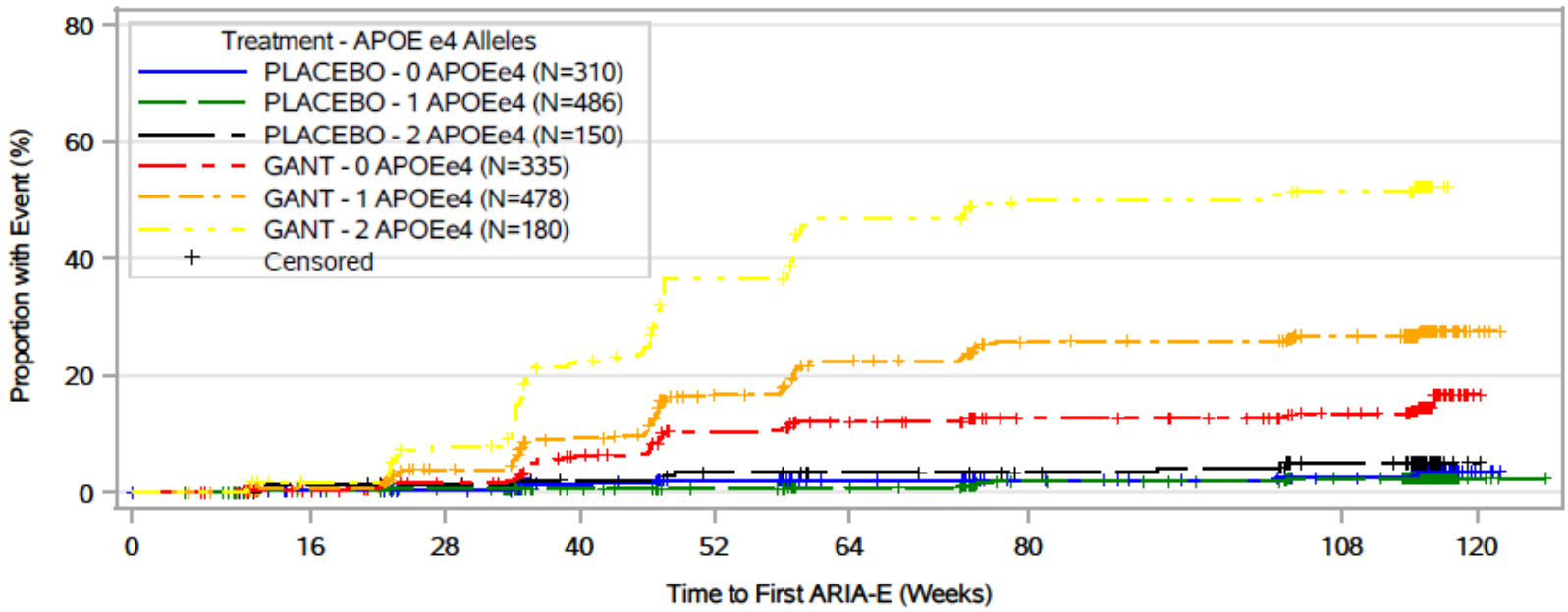
Solid boxes indicate prespecified MRI scanning timepoints for the GRADUATE studies.

eFigure 5. Kaplan-Meier Plot of Time-to-Onset of First ARIA-E Event from First Gantenerumab Dose in Double-Blind Period of GRADUATE Including Open-Label Period and PostGraduate Data



Abbreviations: ARIA-E, amyloid-related imaging abnormalities-edema; D, day; DBL, double-blind; GANT, gantenerumab; W, weeks. Solid boxes indicate prespecified MRI scanning timepoints for the GRADUATE studies (black boxes, double-blind period; grey boxes, open-label period); white boxes indicate MRI scanning timepoints for PostGraduate.

eFigure 6. Kaplan-Meier Plot of Time-to-Onset of First ARIA-E Event in the Double-Blind Period of GRADUATE Trials by APOE ε4 Status

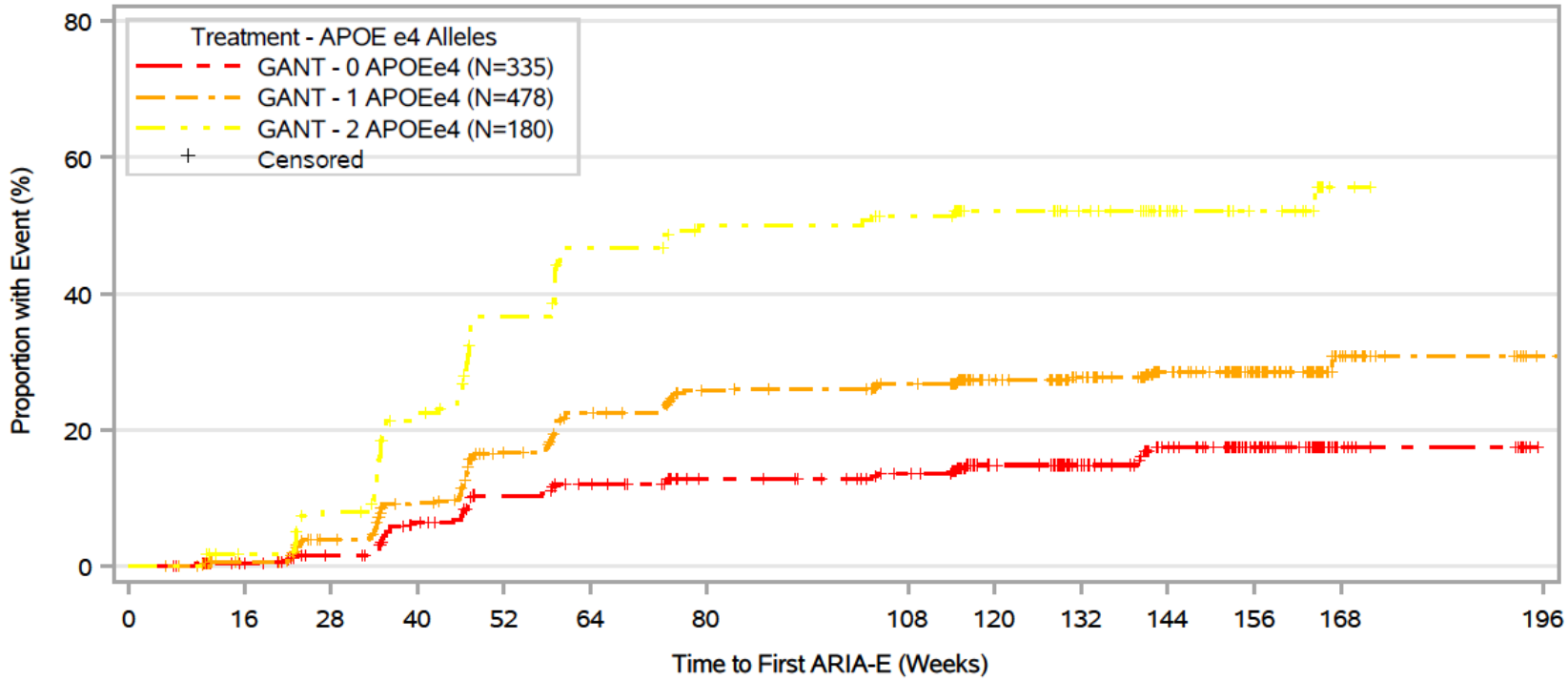


Participants remaining at risk

PLACEBO - 0 APOEe4	310	300	291	277	269	259	244	234	4
PLACEBO - 1 APOEe4	486	475	466	448	438	425	403	387	4
PLACEBO - 2 APOEe4	150	146	142	137	133	129	125	115	1
GANT - 0 APOEe4	335	324	310	287	266	254	234	219	1
GANT - 1 APOEe4	478	463	433	398	350	319	293	277	4
GANT - 2 APOEe4	180	173	160	131	102	83	72	68	NE

Abbreviations: APOE, apolipoprotein E; ARIA-E, amyloid-related imaging abnormalities – edema; GANT, gantenerumab; NE, not evaluable.

eFigure 7. Kaplan-Meier Plot of Time-to-Onset of First ARIA-E Event from First Gantenerumab Dose in Double-Blind Period of GRADUATE Including Open-Label Period and PostGraduate Data by APOE ε4 Status



Participants remaining at risk

GANT - 0 APOEe4	335	324	310	287	266	254	235	222	165	141	113	71	14	NE
GANT - 1 APOEe4	478	463	433	398	350	319	293	279	223	190	151	104	24	2
GANT - 2 APOEe4	180	173	160	131	102	84	73	69	46	39	27	19	2	NE

Abbreviations: APOE, apolipoprotein E; ARIA-E, amyloid-related imaging abnormalities – edema; GANT, gantenerumab; NE, not evaluable.

Supplementary Case Narratives. GRADUATE I and II: Serious Symptomatic ARIA-E Cases

This section includes narratives for episodes of serious symptomatic ARIA-E (ie, where the ARIA-E and/or the CNS symptom temporally associated with the ARIA-E was reported as a serious adverse event [AE]) reported in GRADUATE I and II. Overall, 11 participants randomized to gantenerumab, and none of the participants randomized to placebo, experienced serious symptomatic ARIA-E. These narratives are provided to highlight the clinical presentations, associated imaging findings, and medical interventions applied to manage these cases. While the study protocols mandated study drug suspension for certain ARIA-E findings and permanent study drug discontinuation for exceeding certain cumulative ARIA-H counts (see Supplementary Figure 2), it did not mandate permanent study treatment discontinuation for ARIA-E unless the principal investigator (PI) considered it to be in the best interests of the participant; per the protocol, the study drug could be resumed following the resolution of ARIA-E radiological findings and any associated CNS symptoms. While the study protocol advised that in case of symptomatic ARIA-E, the use of intravenous (IV) corticosteroids may be considered, a specific regimen was not recommended and the specific steroid regimens used were as per the clinician's decision.

276 **Table A. Summary of the Serious Symptomatic ARIA-E Cases**

Characteristic	Results
APOE ε4 status	Six noncarriers, two heterozygous carriers, three homozygous carriers
Late onset, > week 52	Seven of 11 participants
BGTS score > 20	Six of 11 participants
Prominent (> 15 ARIA-H or > 2 SS cumulatively) concurrent new ARIA-H	Seven of 11 participants
Nonserious (asymptomatic or symptomatic) ARIA-E episodes prior to the serious symptomatic ARIA-E episode	Five of 11 participants
Lag between ARIA-E detection and symptoms	Four of 11 participants (4 days, 10 days, approximately 2 weeks, approximately 7 weeks)
Fatal outcome	None
Hospitalizations	10 of 11 participants; three with rehospitalization, of whom one re-hospitalized twice
Restart of study drug	Five of 11 participants; in one case, recurrence of serious ARIA-E on restarting treatment
Treatment with steroids	Eight of 11 participants
Presentation with focal symptoms as described in the case narratives	Four of 11 participants; none received thrombolytics
Seizures reported as AEs	Two of 11 participants: Case 5: numerous seizures (reported as focal dyscognitive seizures) and treatment with multiple anticonvulsants. Case 11: Status epilepticus with 8-point MMSE decline from baseline at early termination visit that improved to a 2-point decline from baseline at week 116.
Additional instances of potential seizure activity as described in the case narratives	Three of 11 participants: Cases 6 and 7: possible seizures treated with anticonvulsants. Case 8: seizure-like episodes.

Clinical course as described in the case narratives	Fluctuating in 3 of 11 participants
Residual symptoms considered potential sequelae according to investigator	One of 11 participants (significant decline in final MMSE, residual significant decline in ADL following ARIA-E and seizure resolution was considered by the investigator as a potential ARIA-E sequelae, albeit confounded by significant MMSE decline trajectory that started before ARIA-E onset)

Abbreviations: ADL, Activities of Daily Living; AE, adverse event; APOE, apolipoprotein E; ARIA-E, amyloid-related imaging abnormalities – edema; ARIA-H, amyloid-related imaging abnormalities – hemosiderosis; BGTS, Barkhof Grand Total Scale; MMSE, Mini-Mental State Examination.

Table B. Summary of the Serious Symptomatic ARIA-E Cases by Maximum ARIA-E Severity

Maximum ARIA-E severity (BGTS)	Number of SS cumulatively upon ARIA-E resolution*	Number of ARIA-H (microhemorrhages and SS) cumulatively upon ARIA-E resolution*
3	0	0
11	0	0
11	0	0
14	3	12
15	0	1
20	4	45
22	3	6
23	1	19
26	5	44
31	6	28
34 (1st episode) 27 (2nd episode)	0 0	8 17

Abbreviations: ARIA-E, amyloid-related imaging abnormalities – edema; ARIA-H, amyloid-related imaging abnormalities – hemosiderosis; BGTS, Barkhof Grand Total Scale; MRI, magnetic resonance imaging; SS, superficial siderosis.

*Cumulative count on the MRI scan that showed radiographic ARIA-E resolution.

Case 1

This 65-year-old White female with prodromal AD had an MMSE score at baseline of 21, was a heterozygous APOE ε4 carrier, and had hyperlipidemia. The screening MRI had no microhemorrhages or SS, and Fazekas score was 1. She was taking donepezil. She was not on any antiplatelets or anticoagulants.

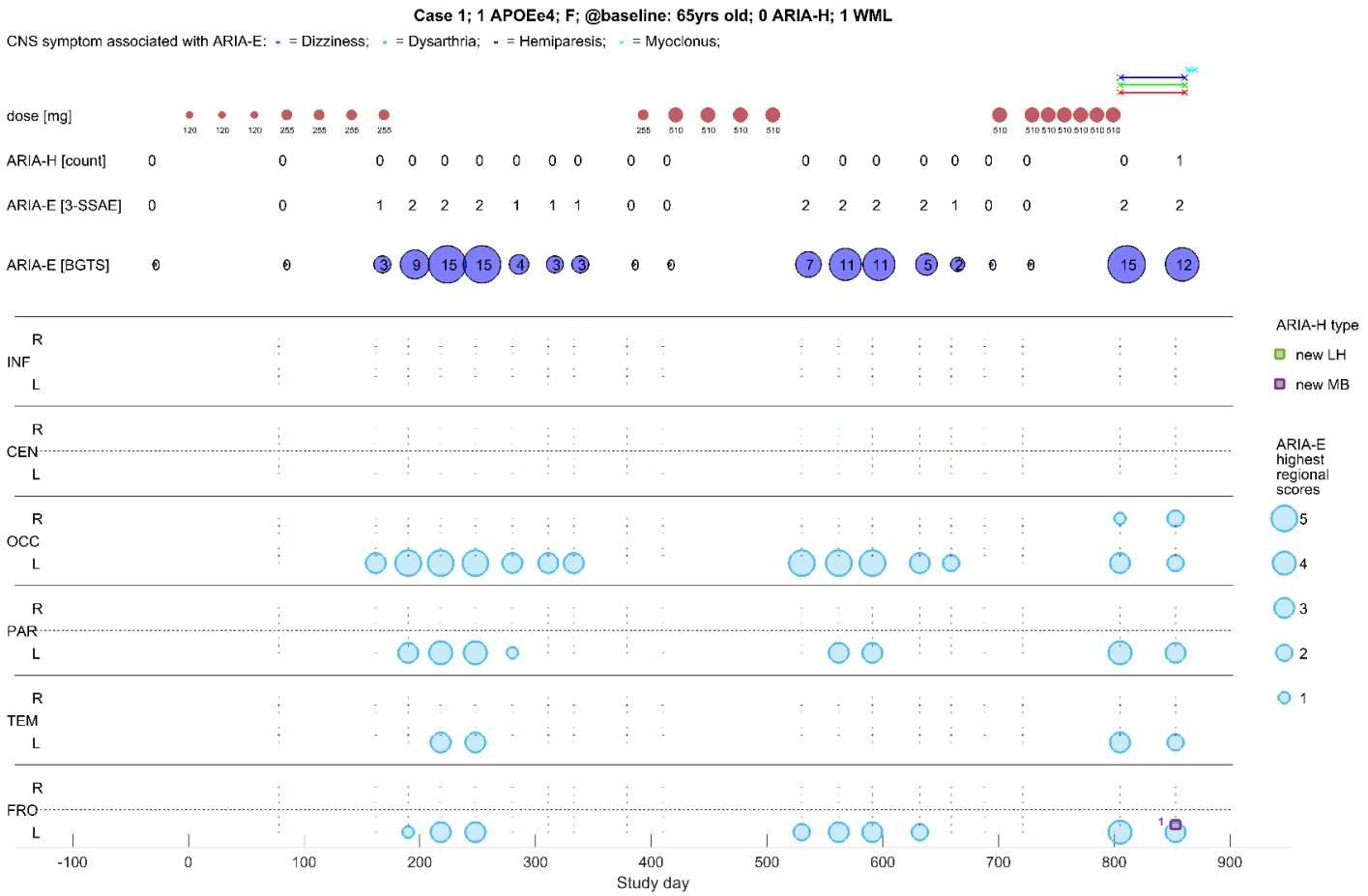
Prior to the serious symptomatic ARIA-E event, she had two asymptomatic ARIA-E episodes, first from study week 24 to week 52 after three doses of 255 mg Q4W gantenerumab, with dosing suspension, with a maximum BGTS of 15, and, following dose resumption, from week 76 to week 100 after one dose of 255 mg and four doses of 510 mg Q4W gantenerumab, with dosing suspension, with a maximum BGTS of 11.

Following gantenerumab dosing resumption, seven gantenerumab doses were administered, including six at the target dose level (510 mg Q2W) prior to the serious symptomatic ARIA-E. Four days after the most recent gantenerumab dose, the scheduled week 116 MRI showed new ARIA-E (BGTS of 15) in the left frontal, left temporal, left parietal, and bilateral occipital regions, without new ARIA-H (see Figure 1 below).

The same day, the participant developed right-sided weakness, dysarthria, and dizziness. Five days later, she presented with these symptoms to the emergency room and was hospitalized. No treatment was given for these events. No further study drug was administered as per the protocol ARIA-E rules, and because the double-blind dosing period was complete. The participant was discharged after 9 days. The ARIA-E symptoms resolved 8 weeks after onset, although the ARIA-E was still present radiologically (BGTS of 12). However, 3 days later, the participant experienced moderate myoclonus of the right hand, for which she was subsequently re-

hospitalized. An MRI scan was repeated locally and reported to be “stable.” The next day (6 days after onset), the myoclonus was considered resolved and the participant was discharged from the hospital without any symptoms. The participant declined further follow-up MRI and therefore the ARIA-E was ongoing at the time that she discontinued from the study. Her last measured MMSE score, at week 116, while the ARIA-E was ongoing, was 14 (7 points lower than baseline and 5 points lower than that at week 76).

The participant’s MRI findings of ARIA observed during the double-blind treatment period of the study are presented below.



324

325 Abbreviations: 3-SSAE, 3-point Severity Scale of ARIA-E; APOE, apolipoprotein E; ARIA-E, amyloid-related imaging abnormalities

326 – edema; ARIA-H, amyloid-related imaging abnormalities – hemosiderosis; BGTS, Barkhof Grand Total Scale; CEN, central region;

327 CNS, central nervous system; FRO, frontal lobe; INF, infratentorial region – on each side of the brain; L, left hemisphere; LH,

leptomeningeal hemosiderosis; MB, microbleed; MRI, magnetic resonance imaging; OCC, occipital lobe; PAR, parietal lobe; R, right hemisphere; TEM, temporal lobe; WML, white matter lesion.

Individual-level ARIA map. The overall radiological severity of ARIA-E is given by the BGTS, which can take values between 0 and 60 and is obtained by summing the highest regional ARIA-E scores across 12 brain regions (FRO, TEM, PAR, OCC, CEN, INF, L, R). The regional ARIA-E scores can take values between 0 and 5. The radiological severity of ARIA-E is rated also with the 3-SSAE-. The radiological severity of ARIA-H is assessed across the same 12 brain regions as ARIA-E and is given by "ARIA-H [count]," the total cumulative number of brain bleeds, which can be of two types, eg, MB and LH. "ARIA-H [count]" at a given MRI visit is the sum between the number of new ARIA-H at that visit and old ARIA-H from all previous MRI visits. The square symbols illustrate only the new ARIA-H at a given MRI visit. The increase in the size of symbols represents an increase in magnitude.

Case 2

This 70-year-old White female with prodromal AD had an MMSE score at baseline of 28, was a non-carrier of APOE ε4, and had hypertension. The screening MRI showed no microhemorrhages or SS, and Fazekas score was 1. She was not on symptomatic AD medication, antiplatelets, or anticoagulants

The Week 24 MRI showed one new microhemorrhage in the left occipital region after three doses of 255 mg Q4W gantenerumab. The Week 28 MRI showed one additional microhemorrhage, in the left frontal region, after the fourth 255 mg dose. She received the first dose of 510 mg Q4W gantenerumab at study week 36. Her most recent MMSE score, at week 24, was 28. A week 40 MRI scan showed new ARIA-E findings (BGTS of 8) in the left temporal, left parietal, and left occipital regions. It also showed five new microhemorrhages in the left occipital region (cumulative ARIA-H count of 7).

Owing to the BGTS ≥ 4, treatment with gantenerumab was temporarily interrupted. Per PI decision, she was hospitalized for further examinations, and received IV methylprednisolone 500 mg once per day (QD) for 5 days for the ARIA-E, with subsequent oral tapering using prednisolone over approximately 6 weeks. An electroencephalogram (EEG) performed during admission was normal. She remained asymptomatic throughout the episode and was discharged from the hospital 1 week after admission. The ARIA-E resolved at week 48 and gantenerumab dosing was resumed.

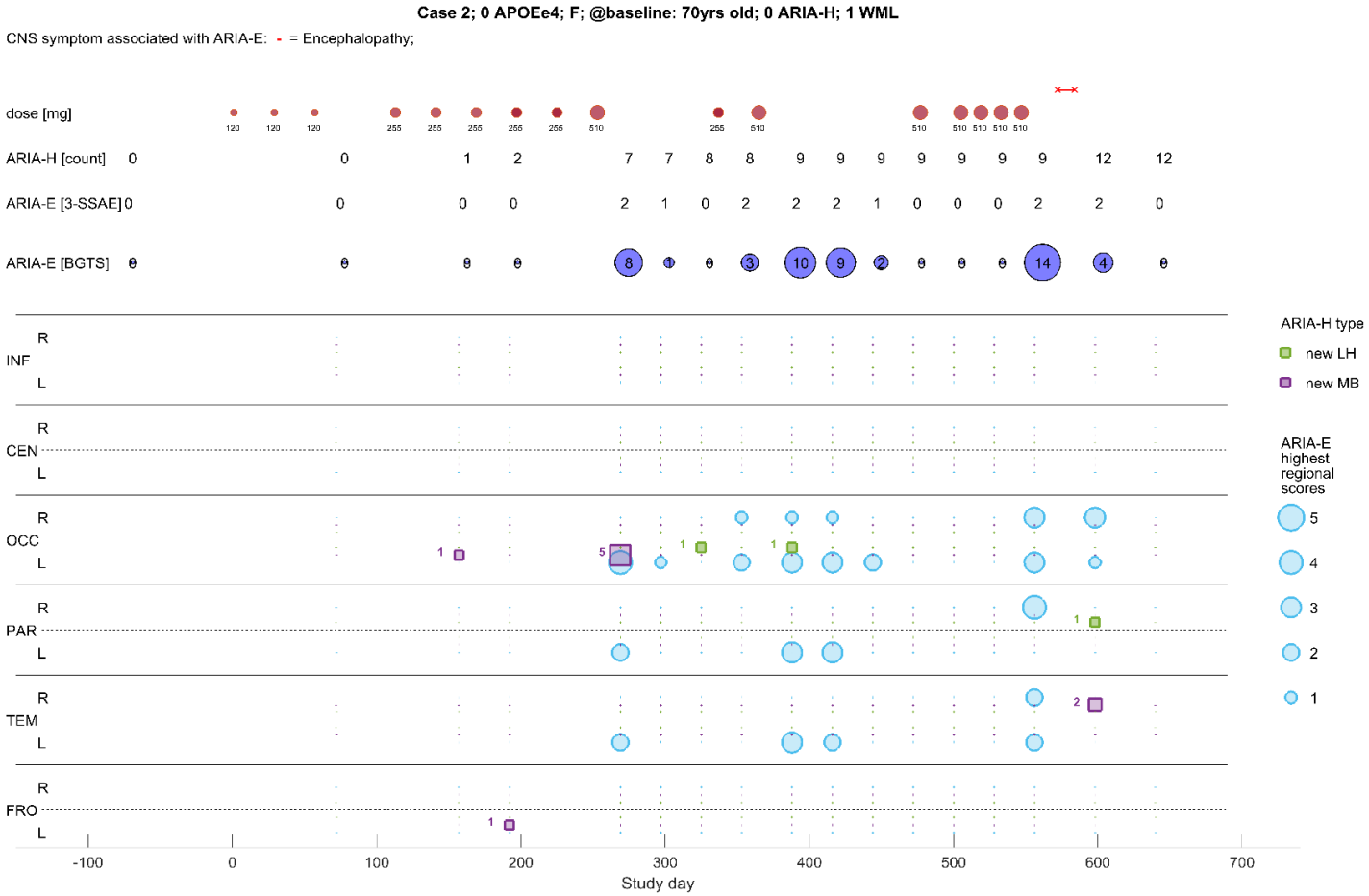
She subsequently had an asymptomatic ARIA-E episode from study week 52 to week 68 following one dose of 255 mg Q4W, with a maximum BGTS severity of 10 and dosing suspension.

Following gantenerumab dosing resumption, five gantenerumab doses, including four at target level (510 mg Q2W) prior to the serious symptomatic ARIA-E were administered, with the most recent at week 78. A week 80 MRI scan showed new ARIA-E (BGTS of 14) in the bilateral occipital, bilateral temporal, and right parietal regions.

Approximately 2 weeks later, the participant experienced a severe headache. She received treatment with ibuprofen and felt partial relief from the headache. A day later, she developed a confusional state. A brain computed tomography (CT) scan showed diffuse occipital, parietal, and posterior frontal hypointensities with no hemorrhages. An EEG showed diffuse alteration of background activity and posterior focal slowing with no epileptiform discharges. She was diagnosed with severe encephalopathy, leading to hospitalization. She was treated with methylprednisolone 1 g QD for 5 days and subsequently switched to a tapering prednisolone dose, starting at 75 mg QD. The encephalopathy resolved approximately 2 weeks after onset, and the participant was discharged. Owing to the ARIA-E and encephalopathy, treatment with blinded study drug was permanently discontinued per the Investigator’s decision.

Two weeks after the encephalopathy resolved, an early termination visit MRI scan showed one new area of SS in the right parietal region and two new microhemorrhages in the right temporal region (cumulative ARIA-H count of 12, including three focal areas of SS). Six weeks after that, the ARIA-E resolved. Her last measured MMSE score, at week 116, was 29 (1 point higher than baseline).

MRI findings of ARIA observed during the double-blind treatment period of the study are presented below.



383

384 Abbreviations: 3-SSAE, 3-point Severity Scale of ARIA-E; APOE, apolipoprotein E; ARIA-E, amyloid-related imaging abnormalities

385 – edema; ARIA-H, amyloid-related imaging abnormalities – hemosiderosis; BGTS, Barkhof Grand Total Scale; CEN, central region;

CNS, central nervous system; FRO, frontal lobe; INF, infratentorial region – on each side of the brain; L, left hemisphere; LH, leptomeningeal hemosiderosis; MB, microbleed; MRI, magnetic resonance imaging; OCC, occipital lobe; PAR, parietal lobe; R, right hemisphere; TEM, temporal lobe; WML, white matter lesion.

Individual-level ARIA map. The overall radiological severity of ARIA-E is given by the BGTS, which can take values between 0 and 60 and is obtained by summing the highest regional ARIA-E scores across 12 brain regions (FRO, TEM, PAR, OCC, CEN, INF, L, R). The regional ARIA-E scores can take values between 0 and 5. The radiological severity of ARIA-E is rated also with the 3-SSAE The radiological severity of ARIA-H is assessed across the same 12 brain regions as ARIA-E and is given by "ARIA-H [count]," the total cumulative number of brain bleeds, which can be of two types, eg., MB and LH. "ARIA-H [count]" at a given MRI visit is the sum between the number of new ARIA-H at that visit and old ARIA-H from all previous MRI visits. The square symbols illustrate only the new ARIA-H at a given MRI visit. The increase in the size of symbols represents an increase in magnitude.

Case 3

This 79-year-old White female with prodromal AD had an MMSE score at baseline of 20, was a non-carrier of APOE ε4, and had hypercholesterolemia. The screening MRI showed no microhemorrhages or SS, and Fazekas score was 0. She was not on symptomatic AD medication, antiplatelets, or anticoagulants.

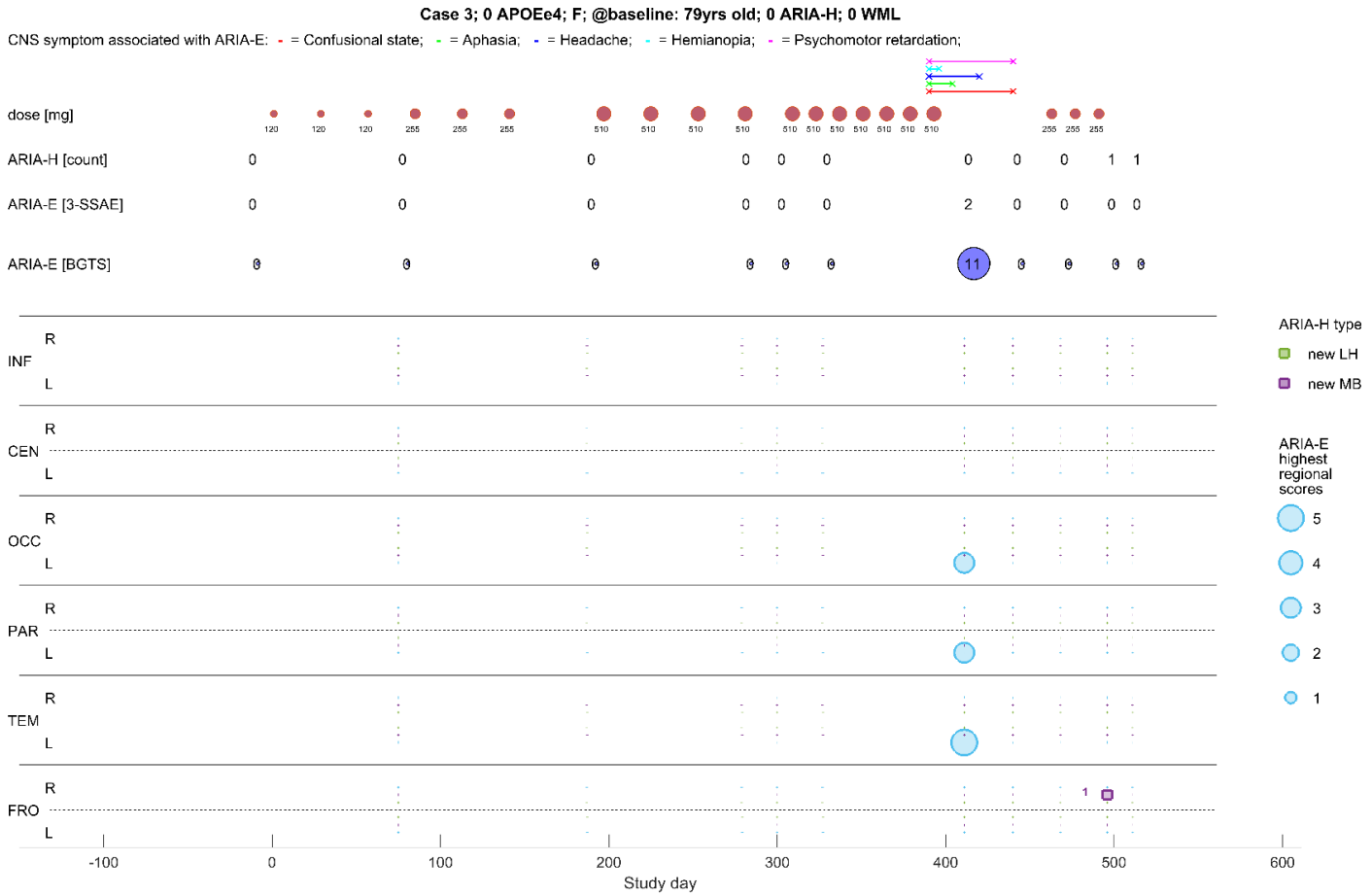
At week 52, her MMSE score was 22. At week 56, hours from the administration of the seventh target gantenerumab dose (510 mg Q2W subcutaneous [SC]), the participant experienced headache, nausea, vomiting, confusional state, psychomotor retardation, aphasia, and ipsilateral right hemianopia (the latter two severe), and was hospitalized. A CT scan showed hypodensity and loss of left temporoparietal cortico-subcortical differentiation with mass effect on the occipital lobe of the ipsilateral left ventricle and obliteration of adjacent convexity grooves, without objective pathological uptake of IV contrast. The radiology report stated findings were suggestive of acute ischemic injury in the territory supplied by posterior branches of the left middle cerebral artery. As the treating physician's diagnosis was ARIA-E, the participant received treatment with dexamethasone 18 mg daily, which was subsequently tapered. No thrombolytic was given. ARIA-E was subsequently (3 weeks later) confirmed on a per-protocol week 60 MRI scan in the left temporal, left parietal, and left occipital area (BGTS of 11). Study drug dosing was interrupted due to the symptomatic ARIA-E.

While in hospital, 1 day after admission, the participant experienced elevated blood pressure of 180/75 mmHg, reported by the investigator as a hypertensive crisis, which prolonged her hospitalization. The investigator considered the hypertensive episode to be related to the blinded study drug. She received treatment with amlodipine and

losartan. On the same day, the events of nausea and vomiting were considered resolved.

Five days later, the hemianopia was considered resolved. After a further 5 days, the hypertensive episode was considered resolved and the participant was discharged. After a further 3 days, the aphasia was also considered resolved. Approximately 2 weeks after that, the headache was considered resolved. After an additional 3 weeks, the confusional state and psychomotor retardation were also considered resolved. On the same day, a week 64 MRI scan revealed no ARIA-E findings, leading to gantenerumab resumption at week 66 for three further doses of 255 mg Q2W, without ARIA-E recurrence. Her last measured MMSE score, at the early termination visit, was 19 (1 point lower than baseline).

MRI findings of ARIA observed during the double-blind treatment period of the study are presented below.



432

433 Abbreviations: 3-SSAE, 3-point Severity Scale of ARIA-E; APOE, apolipoprotein E; ARIA-E, amyloid-related imaging abnormalities

434 – edema; ARIA-H, amyloid-related imaging abnormalities – hemosiderosis; BGTS, Barkhof Grand Total Scale; CEN, central region;

435 CNS, central nervous system; FRO, frontal lobe; INF, infratentorial region – on each side of the brain; L, left hemisphere; LH,

leptomeningeal hemosiderosis; MB, microbleed; MRI, magnetic resonance imaging; OCC, occipital lobe; PAR, parietal lobe; R, right hemisphere; TEM, temporal lobe; WML, white matter lesion.

Individual-level ARIA map. The overall radiological severity of ARIA-E is given by the BGTS, which can take values between 0 and 60 and is obtained by summing the highest regional ARIA-E scores across 12 brain regions (FRO, TEM, PAR, OCC, CEN, INF, L, R). The regional ARIA-E scores can take values between 0 and 5. The radiological severity of ARIA-E is rated also with the 3-SSAE The radiological severity of ARIA-H is assessed across the same 12 brain regions as ARIA-E and is given by “ARIA-H [count],” the total cumulative number of brain bleeds, which can be of two types, eg, MB and LH. “ARIA-H [count]” at a given MRI visit is the sum between the number of new ARIA-H at that visit and old ARIA-H from all previous MRI visits. The square symbols illustrate only the new ARIA-H at a given MRI visit. The increase in the size of symbols represents an increase in magnitude.

Case 4

This 76-year-old White female with prodromal AD had an MMSE score at baseline of 21, was a non-carrier of APOE ε4, and had a history of transient ischemic attack, increased blood cholesterol, being overweight, tension headache, and migraine. The screening MRI did not show microhemorrhages or SS, and Fazekas score was 1. She was not on symptomatic AD medication. She received an antiplatelet (acetylsalicylic acid 81 mg QD) but not an anticoagulant.

Prior to the serious symptomatic ARIA-E event, she had two ARIA-E episodes; first, non-serious symptomatic (migraine) from study week 12 to week 24 following three doses of 120 mg Q4W gantenerumab, with a maximum BGTS of 3 and continuation of study drug, and second, asymptomatic from week 48 to week 56 following three doses of 510 mg Q4W gantenerumab, with a maximum BGTS of 3 and continuation of study drug.

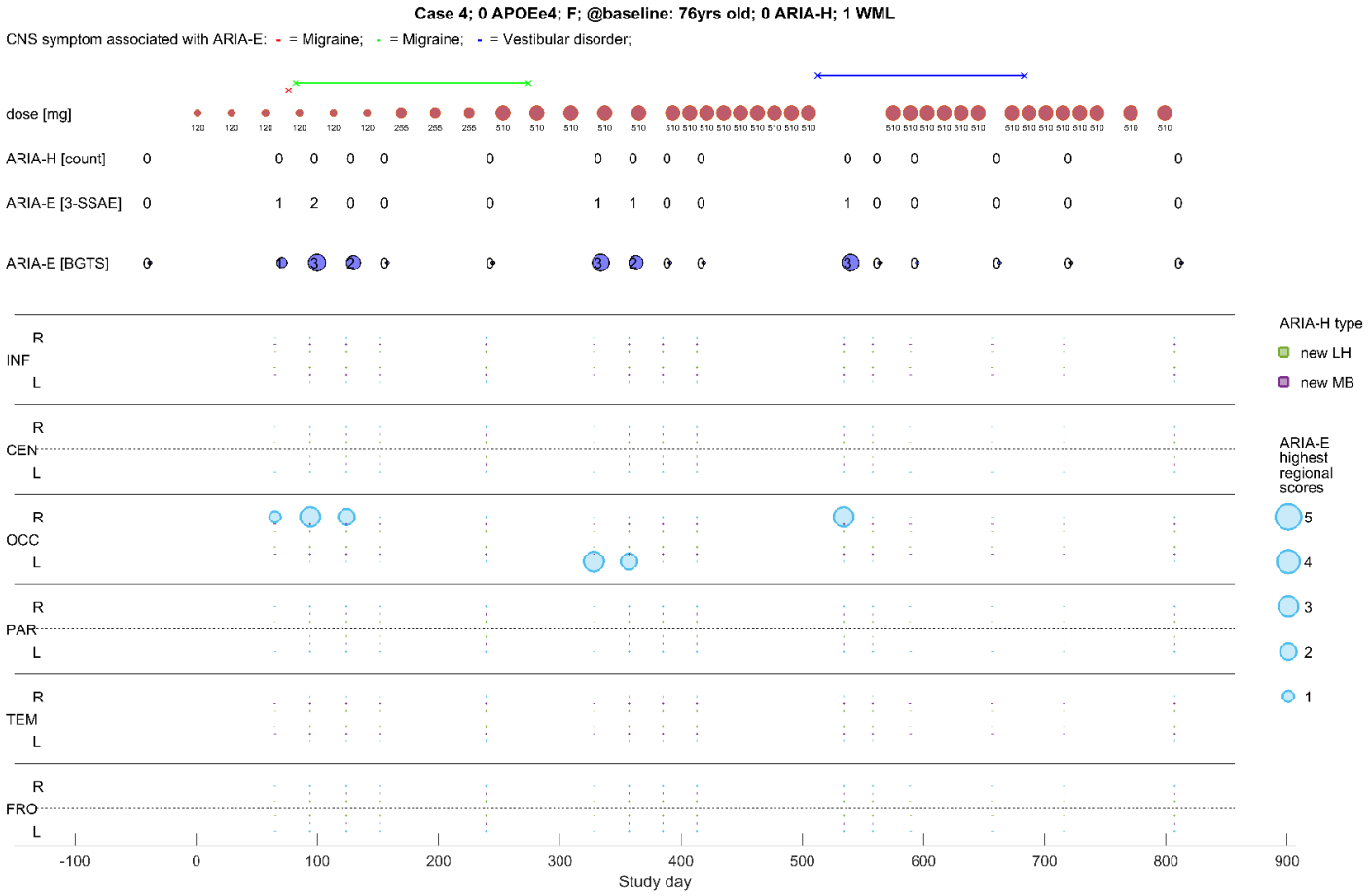
Her MMSE score measured at week 52 was 22. At week 72, she received the 9th target dose of 510 mg Q2W gantenerumab. Ten days later, the participant experienced intermittent dizziness and lightheadedness while walking and being upright but not in the supine or sitting positions. It was also reported that her voice had been hoarse. Vital signs showed blood pressure 130/70 mmHg, with no postural drop. On the same day, she was diagnosed with severe vestibular disorder. Five days later, a CT scan was negative for acute findings; it, however, showed moderate chronic small vessel disease. A non-study MRI scan on the same day showed mild global parenchymal loss and extensive white matter hyperintensity, and right occipital encephalomalacia. On the same day, the participant was hospitalized. She received treatment with meclizine for the vestibular disorder. Labyrinthitis secondary to a recent

ear lavage for excessive cerumen was suspected. A day after admission, symptoms improved, and she was discharged. Approximately 2 weeks after hospital discharge, the scheduled week 76 MRI scan showed new ARIA-E (BGTS of 3) in the right occipital region.

The investigator considered the vestibular dysfunction to be related to blinded study drug and ear lavage for excessive cerumen. Subsequently, the scheduled week 80 MRI scan showed radiological resolution of the ARIA-E. Owing to the ARIA-E and vestibular dysfunction, treatment with gantenerumab was suspended after week 72 and the next dose was given at week 82.

Approximately 14 weeks after the ARIA-E resolved, the participant started ambulating with a cane to minimize fall risk. Four weeks later, vestibular disorder was considered resolved when cane use was no longer necessary. Her last measured MMSE score, at week 116, was 21 (no change since baseline).

MRI findings of ARIA observed during the double-blind treatment period of the study are presented below.



484

485 Abbreviations: 3-SSAE, 3-point Severity Scale of ARIA-E; APOE, apolipoprotein E; ARIA-E, amyloid-related imaging abnormalities

486 – edema; ARIA-H, amyloid-related imaging abnormalities – hemosiderosis; BGTS, Barkhof Grand Total Scale; CEN, central region;

487 CNS, central nervous system; FRO, frontal lobe; INF, infratentorial region – on each side of the brain; L, left hemisphere; LH,

leptomeningeal hemosiderosis; MB, microbleed; MRI, magnetic resonance imaging; OCC, occipital lobe; PAR, parietal lobe; R, right hemisphere; TEM, temporal lobe; WML, white matter lesion.

Individual-level ARIA map. The overall radiological severity of ARIA-E is given by the BGTS, which can take values between 0 and 60 and is obtained by summing the highest regional ARIA-E scores across 12 brain regions (FRO, TEM, PAR, OCC, CEN, INF, L, R). The regional ARIA-E scores can take values between 0 and 5. The radiological severity of ARIA-E is rated also with the 3-SSAE The radiological severity of ARIA-H is assessed across the same 12 brain regions as ARIA-E and is given by “ARIA-H [count],” the total cumulative number of brain bleeds, which can be of two types, eg, MB and LH. “ARIA-H [count]” at a given MRI visit is the sum between the number of new ARIA-H at that visit and old ARIA-H from all previous MRI visits. The square symbols illustrate only the new ARIA-H at a given MRI visit. The increase in the size of symbols represents an increase in magnitude.

Case 5

This 60-year-old White male with prodromal AD had an MMSE score at baseline of 18, was a heterozygous APOE ε4 carrier, and had hypertension and hypercholesterolemia. The screening MRI had no microhemorrhages or SS, and Fazekas score was 1. He was on donepezil. He was not on an antiplatelet or anticoagulant.

His most recent post-baseline MMSE score before ARIA-E development, at week 76, was 8. He received the 16th target dose of 510 mg Q2W gantenerumab at week 82. Five days later, the participant received an influenza vaccine (INACT SAG 3V) and after 30 minutes showed stroke-like symptoms, with weakness on one side, slight tremors, and slurred speech. On the same day, an unscheduled MRI scan showed new ARIA-E (BGTS of 11) in the left frontal, left occipital, left parietal, and left temporal regions.

The MRI scan also showed increased white matter signals in the left occipital lobe in similar distribution as seen in a prior CT scan, with minimal blush of enhancement and mild restricted diffusion in the cortex of the same region with no evidence of an underlying mass, suggestive of postictal changes. A CT angiography of the brain/neck stroke perfusion showed vasogenic edema in the left occipital lobe, which represented a leptomeningeal pathology versus intraparenchymal lesion. The participant was diagnosed with severe focal dyscognitive seizures, resulting in hospitalization. Owing to the symptomatic ARIA-E, treatment with blinded study drug was suspended. An EEG was indicative of epileptogenicity in the left posterior temporal region, and severe diffuse encephalopathy and epileptogenicity in the left posterior region. In addition, numerous electrographic and electroclinical seizures were captured. The participant

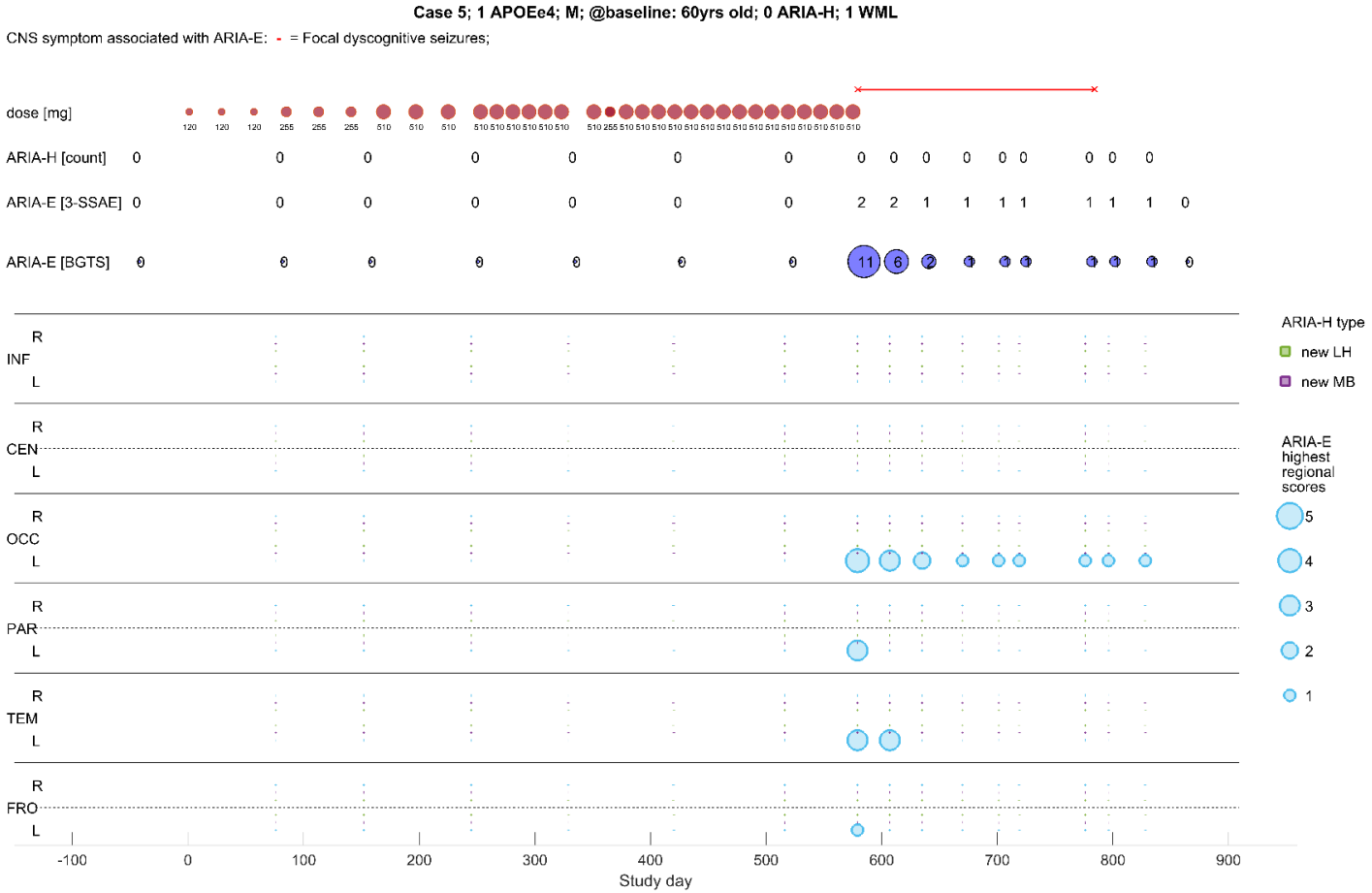
received treatment with midazolam and fosphenytoin for the focal dyscognitive seizures, and heparin for prophylaxis.

An EEG a day later showed ongoing electroclinical seizures and the participant was treated with levetiracetam, valproic acid, lacosamide, and methylprednisolone (1 g QD for 2 days). One day later, dexamethasone was added (26 mg QD for 1 day, followed by tapering over approximately 4 weeks). One day later, EEG results were consistent with previous results and sodium valproate was commenced. A day later, with continued electroconvulsive seizures captured, he received treatment with oxcarbazepine and clobazam. Two days later, the EEG recording improved with no seizure seen, and he was discharged from the hospital. It was reported that he continued to have some behavioral signs of seizure activity, eg, looking to the side, inappropriate laughter, episodes of staring blankly, and he continued to have aphasia. He was no longer able to drive or know his way around the neighborhood. He could no longer bathe himself, use the toilet properly although he was continent, and could not make himself food or get himself a drink. He had a hard time responding to commands and became visibly frustrated.

Approximately 10 weeks after the hospital discharge, the participant experienced mild affective disorder, for which he received treatment with escitalopram. Approximately 15 weeks after that (week 104), his MMSE score was 7. Approximately 3 weeks later, the EEG showed no seizures; episodes of spike and slow wave were noted in the left temporal and parietal areas, occasionally bilaterally. On the same day, the focal dyscognitive seizures were considered resolved with sequelae. The PI reported that damage from the seizures and resultant inflammation made it difficult, if not impossible. for the AD brain to heal. The PI considered it difficult to parse out the

contribution of the ARIA-E from the underlying AD and seizures that occurred. Approximately 16 weeks later, an unscheduled MRI scan revealed no ARIA-E findings. The event of affective disorder was unresolved at the time of study completion. His last measured MMSE score, at week 116, was 3 (15 points lower than baseline).

MRI findings of ARIA observed during the double-blind treatment period of the study are presented below.



551

552 Abbreviations: 3-SSAE, 3-point Severity Scale of ARIA-E; APOE, apolipoprotein E; ARIA-E, amyloid-related imaging abnormalities

553 – edema; ARIA-H, amyloid-related imaging abnormalities – hemosiderosis; BGTS, Barkhof Grand Total Scale; CEN, central region;

554 CNS, central nervous system; FRO, frontal lobe; INF, infratentorial region – on each side of the brain; L, left hemisphere; LH,

leptomeningeal hemosiderosis; MB, microbleed; MRI, magnetic resonance imaging; OCC, occipital lobe; PAR, parietal lobe; R, right hemisphere; TEM, temporal lobe; WML, white matter lesion.

Individual-level ARIA map. The overall radiological severity of ARIA-E is given by the BGTS, which can take values between 0 and 60 and is obtained by summing the highest regional ARIA-E scores across 12 brain regions (FRO, TEM, PAR, OCC, CEN, INF, L, R). The regional ARIA-E scores can take values between 0 and 5. The radiological severity of ARIA-E is rated also with the 3-SSAE The radiological severity of ARIA-H is assessed across the same 12 brain regions as ARIA-E and is given by “ARIA-H [count],” the total cumulative number of brain bleeds, which can be of two types, eg, MB and LH. “ARIA-H [count]” at a given MRI visit is the sum between the number of new ARIA-H at that visit and old ARIA-H from all previous MRI visits. The square symbols illustrate only the new ARIA-H at a given MRI visit. The increase in the size of symbols represents an increase in magnitude.

Case 6

This 72-year-old White male with prodromal AD had an MMSE score at baseline of 28, was a non-carrier of APOE ε4, and had hypercholesterolemia. The screening MRI did not show microhemorrhages or SS, and Fazekas score was 0. He was on donepezil. He was not on an antiplatelet or anticoagulant.

Prior to the serious symptomatic ARIA-E event, he had an asymptomatic ARIA-E episode from study week 36 to week 44, following two doses of 510 mg gantenerumab Q4W, with a maximum BGTS severity of 4 and dosing suspension. At week 36, he also had three new ARIA-H findings (one microhemorrhage and two focal areas of SS).

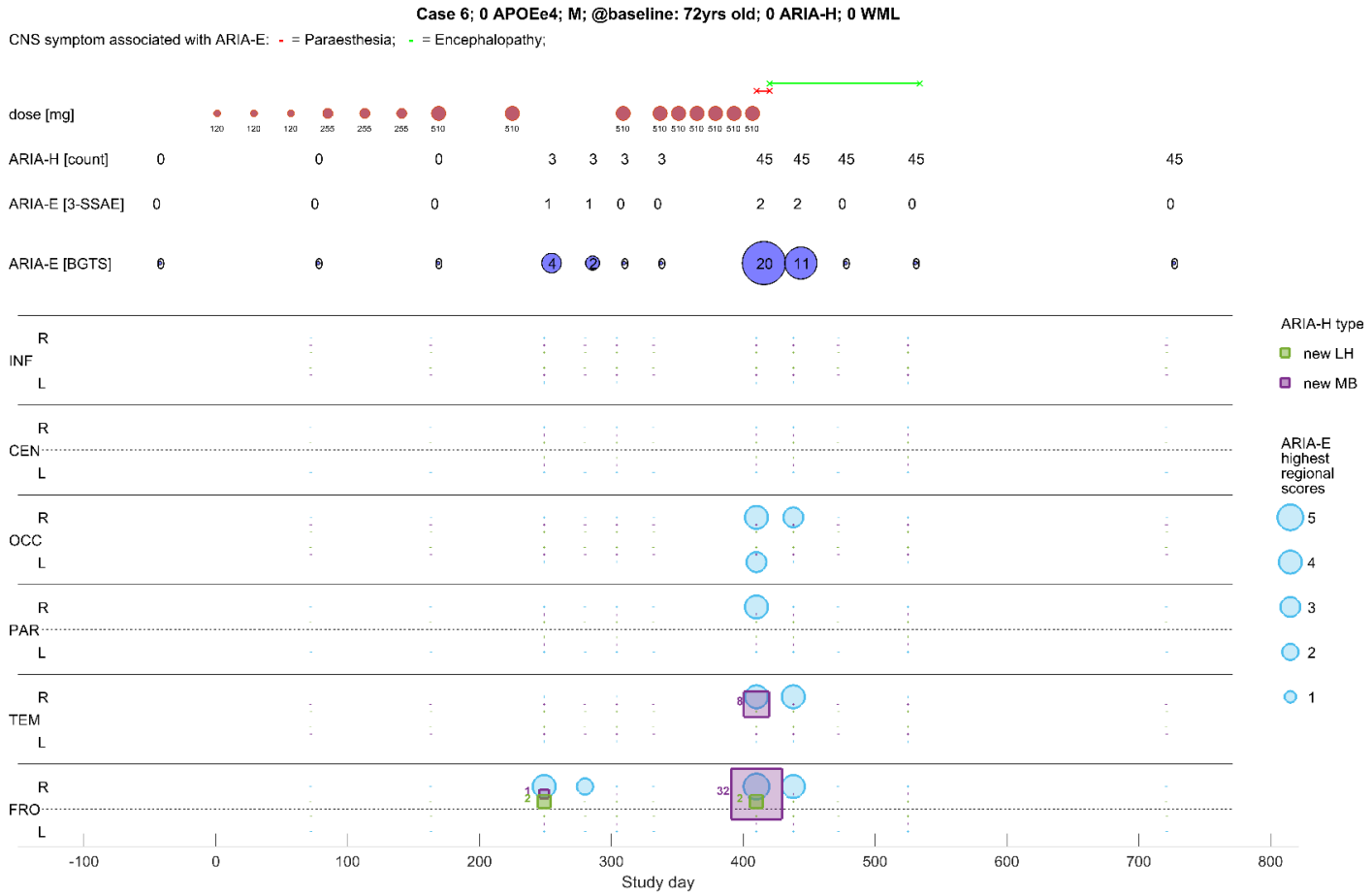
His most recent MMSE score, at week 52, was 22. Following gantenerumab dose resumption, seven gantenerumab doses, including six at target level (510 mg Q2W) were administered prior to the serious symptomatic ARIA-E, with the most recent dose at week 58. One day later, the scheduled week 60 MRI scan showed 40 new microhemorrhages in the right frontal and right temporal regions and two new areas of SS in the right frontal region (cumulative ARIA-H of 45). This MRI scan also showed new ARIA-E findings (BGTS of 20) in the right frontal, bilateral occipital, right parietal, and right temporal regions.

In addition, within 24 hours after the end of injection, the participant experienced mild paresthesia in the fingers of both hands. No treatment was given for the paresthesia. Owing to the week 60 finding of 45 ARIA-H cumulatively, treatment with gantenerumab was permanently discontinued as required per the study protocol.

Ten days after ARIA-E detection, the participant became incoherent and was taken to the emergency room. On the same day, the event of paresthesia was considered resolved. One day later, the participant was more confused throughout the day. He had spells of staring off into space for around 30 seconds and he would not respond to inquiry. The following day, he was hospitalized to rule out stroke and urinary tract infection (UTI). At the time of admission, he was noted with word-finding difficulty, fluctuations in orientation, inattention, and intermittent confusion. A chest X-ray and an ultrasound showed negative results. A head CT scan showed right frontal and parieto-occipital swelling. Continuous EEG showed focal slowing in the right hemisphere, indicating focal cerebral dysfunction and mild-to-moderate generalized slowing. Locally performed brain MRI showed nonspecific findings that were likely ARIA-E and ARIA-H primarily throughout the right hemisphere (scan not available to the Sponsor). The participant was diagnosed with encephalopathy and assessed by the investigator as related to the blinded study drug. The participant received treatment with quetiapine and levetiracetam. He further received treatment with IV methylprednisolone 1 g QD for 4 days for the ARIA-E, leading to only minimal improvement. Six days after admission, he was discharged from the hospital.

Approximately 6 weeks after the hospital discharge, an early termination MRI scan revealed no ARIA-E findings. It was reported that all his symptoms resolved after approximately 16 weeks from onset. His last measured MMSE score, at week 116, was 20 (8 points lower than at baseline).

MRI findings of ARIA observed during the double-blind treatment period of the study are presented below.



609

610 Abbreviations: 3-SSAE, 3-point Severity Scale of ARIA-E; APOE, apolipoprotein E; ARIA-E, amyloid-related imaging abnormalities

611 – edema; ARIA-H, amyloid-related imaging abnormalities – hemosiderosis; BGTS, Barkhof Grand Total Scale; CEN, central region;

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leptomeningeal hemosiderosis; MB, microbleed; MRI, magnetic resonance imaging; OCC, occipital lobe; PAR, parietal lobe; R, right hemisphere; TEM, temporal lobe; WML, white matter lesion.

Individual-level ARIA map. The overall radiological severity of ARIA-E is given by the BGTS, which can take values between 0 and 60 and is obtained by summing the highest regional ARIA-E scores across 12 brain regions (FRO, TEM, PAR, OCC, CEN, INF, L, R). The regional ARIA-E scores can take values between 0 and 5. The radiological severity of ARIA-E is rated also with the 3-SSAE The radiological severity of ARIA-H is assessed across the same 12 brain regions as ARIA-E and is given by “ARIA-H [count],” the total cumulative number of brain bleeds, which can be of two types, eg, MB and LH. “ARIA-H [count]” at a given MRI visit is the sum between the number of new ARIA-H at that visit and old ARIA-H from all previous MRI visits. The square symbols illustrate only the new ARIA-H at a given MRI visit. The increase in the size of symbols represents an increase in magnitude.

Case 7

This 77-year-old White female with prodromal AD had an MMSE score at baseline of 24, was a homozygous APOE ε4 carrier, and had no relevant medical history. The screening MRI revealed one microhemorrhage in the left temporal region and one area of SS in the right frontal region, and Fazekas score was 2. She was not on symptomatic AD medication, an antiplatelet, or anticoagulant.

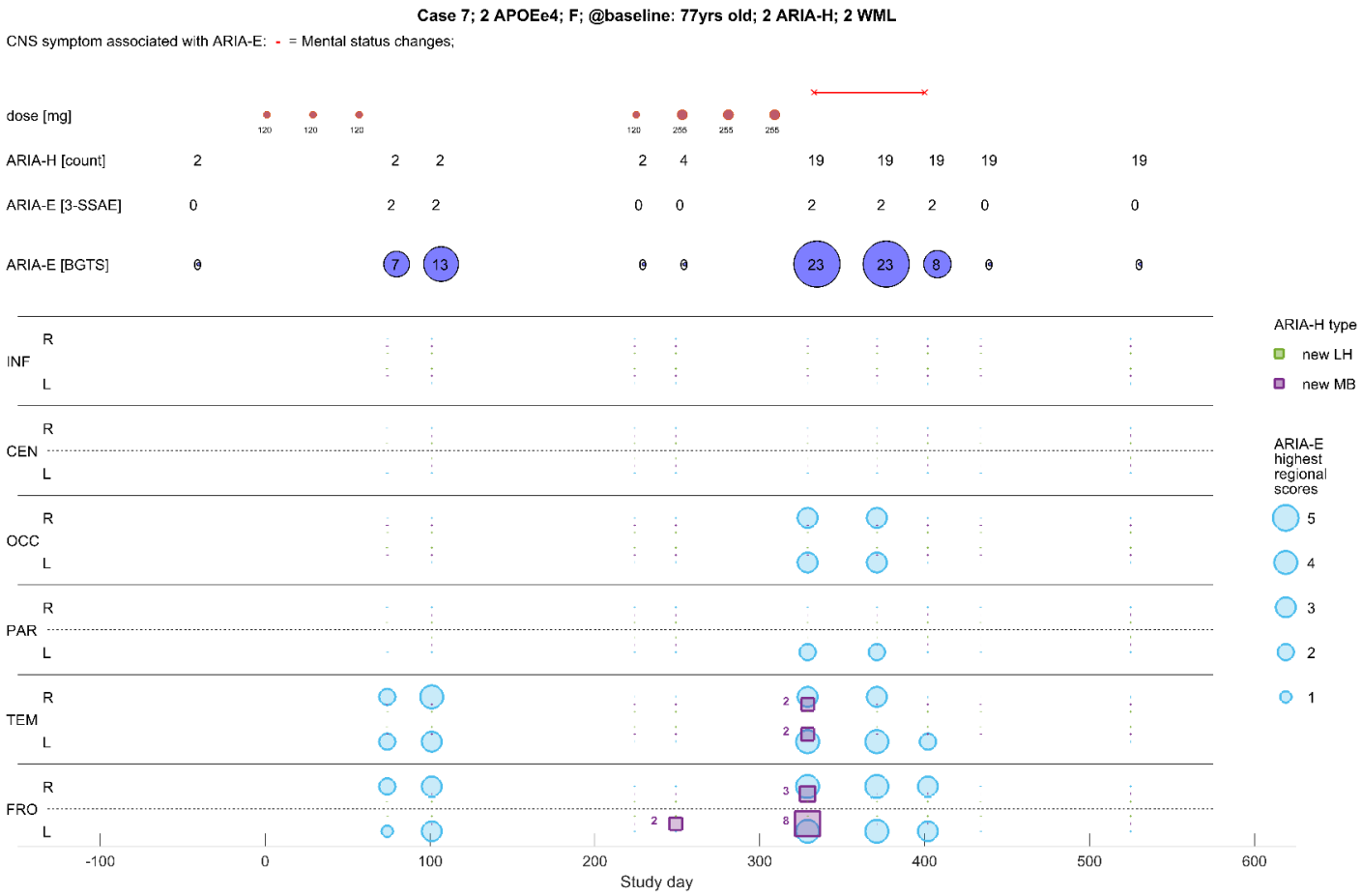
Prior to the serious symptomatic ARIA-E event, she had an asymptomatic ARIA-E episode from study week 12 to week 32 after three doses of 120 mg Q4W gantenerumab, with a maximum BGTS of 13 and dosing suspension. At week 36, she had two new microhemorrhages.

Following gantenerumab dose resumption, four gantenerumab doses, including three at the 255 mg Q2W level, were administered prior to the serious symptomatic ARIA-E, with the most recent dose at week 44. Approximately 3 weeks later, the scheduled week 48 MRI scan showed 15 new microhemorrhages in the bilateral temporal and bilateral frontal regions (cumulative ARIA-H of 19). It also showed new ARIA-E (BGTS of 23) in the bilateral frontal, bilateral occipital, bilateral temporal, and left parietal regions.

Owing to the week 48 finding of 19 ARIA-H cumulatively, treatment with gantenerumab was permanently discontinued as required per the study protocol. Four days later, the participant experienced confusion and was diagnosed with severe mental status changes. She was hospitalized to rule out a cerebrovascular accident. A laboratory workup showed a normal level of electrolytes with no infection. A head CT scan showed no acute intracranial abnormality. An MRI scan was consistent with severe multifocal ARIA-E and ARIA-H (scan not available to the Sponsor). On the next day,

her mental state worsened as she was not responding to any commands other than opening her eyes. A repeat CT scan of the head showed multiple areas of vasogenic edema in both cerebral hemispheres. CSF analysis revealed no abnormal findings. An EEG showed intermittent left hemisphere slowing and moderate generalized slowing with triphasic waves, indicative of diffuse cerebral dysfunction. She received treatment with magnesium sulfate. She was also treated with ceftriaxone for mild UTI, based on urinalysis. Cognition improved and she was discharged to a rehabilitation facility; she was switched to cephalexin for the UTI. Over the next 2 days, her cognition fluctuated in the context of fever (body temperature of 100.5 °F). A repeat culture showed the presence of pan-sensitive E. coli and the participant was switched back to ceftriaxone. Two days after the hospital discharge, she became afebrile, and her mental status returned to baseline. On the suspicion that seizures might have accounted for her episodic mental status changes, treatment with levetiracetam and corticosteroids (regimen details not provided to the Sponsor) was started by the rehabilitation team after consulting the neurologist. Approximately 2 weeks later, she was discharged from the rehabilitation center. After a further, approximately, 7 weeks, her MMSE score was 25 and the event of mental status changes was considered resolved. Approximately 4 weeks after that, MRI revealed no ARIA-E findings. Her last measured MMSE score, at week 116, was 22 (2 points lower than at baseline).

MRI findings of ARIA observed at screening and during the double-blind treatment period of the study are presented below.



667

668 Abbreviations: 3-SSAE, 3-point Severity Scale of ARIA-E; APOE, apolipoprotein E; ARIA-E, amyloid-related imaging abnormalities

669 – edema; ARIA-H, amyloid-related imaging abnormalities – hemosiderosis; BGTS, Barkhof Grand Total Scale; CEN, central region;

670 CNS, central nervous system; FRO, frontal lobe; INF, infratentorial region – on each side of the brain; L, left hemisphere; LH,

leptomeningeal hemosiderosis; MB, microbleed; MRI, magnetic resonance imaging; OCC, occipital lobe; PAR, parietal lobe; R, right hemisphere; TEM, temporal lobe; WML, white matter lesion.

Individual-level ARIA map. The overall radiological severity of ARIA-E is given by the BGTS, which can take values between 0 and 60 and is obtained by summing the highest regional ARIA-E scores across 12 brain regions (FRO, TEM, PAR, OCC, CEN, INF, L, R). The regional ARIA-E scores can take values between 0 and 5. The radiological severity of ARIA-E is rated also with the 3-SSAE The radiological severity of ARIA-H is assessed across the same 12 brain regions as ARIA-E and is given by “ARIA-H [count],” the total cumulative number of brain bleeds, which can be of two types, eg, MB and LH. “ARIA-H [count]” at a given MRI visit is the sum between the number of new ARIA-H at that visit and old ARIA-H from all previous MRI visits. The square symbols illustrate only the new ARIA-H at a given MRI visit. The increase in the size of symbols represents an increase in magnitude.

Case 8

This 77-year-old White male with prodromal AD had an MMSE score at baseline of 24, was a non-carrier of APOE ε4, and had type 2 diabetes, hypercholesterolemia, and hypertension. The screening MRI revealed one area of SS in the right parietal region, and Fazekas score was 1. He was not on symptomatic AD medication. He was on acetylsalicylic acid (325 mg QD) but not on anticoagulants.

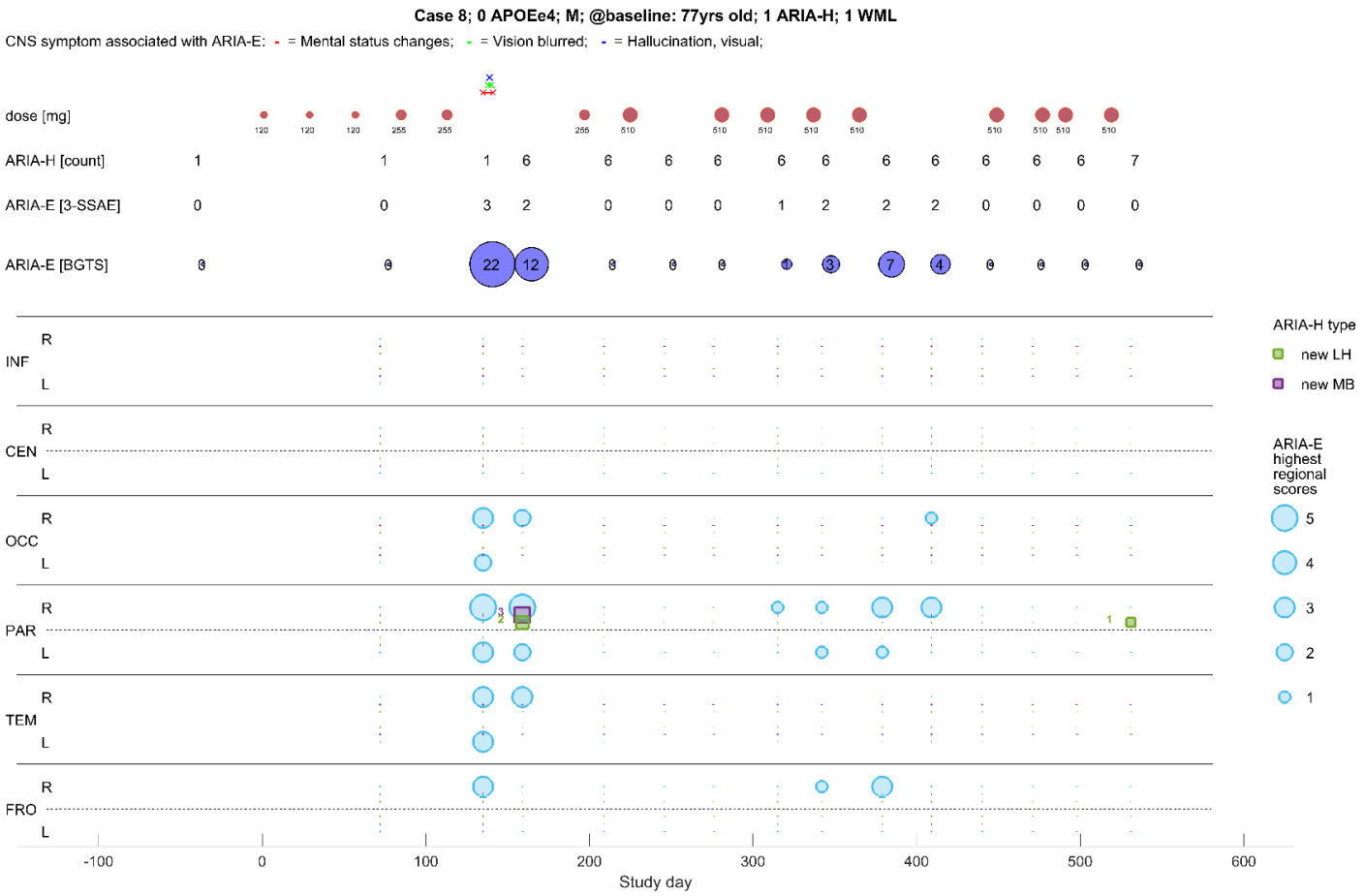
The most recent dose of gantenerumab prior to the serious symptomatic ARIA-E event was administered at week 16 (second dose of 255 mg Q4W). Three weeks later, the participant experienced increased confusion, brief seizure-like activity, and was reported to be “bumping into things.” A brain CT showed cerebral edema and an unscheduled brain MRI scan showed ARIA-E (BGTS of 22) in the right frontal, bilateral temporal, bilateral parietal, and bilateral occipital regions.

Owing to the BGTS ≥ 4, treatment with gantenerumab was suspended. The participant received treatment with methylprednisolone for the ARIA-E (1 g QD for 2 days). The participant then experienced mild blurring of vision and visual hallucinations, which both resolved without any treatment. The mental status changes resolved over 6 days, and he was discharged from the hospital.

Approximately 3 weeks later, MRI showed that the ARIA-E decreased (BGTS 12), but there were three new microhemorrhages and two new areas of SS in the right parietal region (cumulative ARIA-H count of 6); and week 24 MMSE score was 20 (4 points lower than at baseline). Approximately 7 weeks after that, the scheduled MRI scan showed no ARIA-E findings, leading to gantenerumab resumption.

After a further four gantenerumab doses, including three at 510 mg Q4W level, the participant experienced ARIA-E recurrence between study week 48 and week 64 (asymptomatic; maximum BGTS of 7, leading to dosing suspension). After the ARIA-E resolved, gantenerumab was again resumed, for a further four doses of 510 mg Q4W, without ARIA-E recurrence, but treatment was then permanently discontinued after the scheduled week 76 MRI scan for accumulating four focal areas of SS cumulatively (a protocol criterion for permanent study drug discontinuation). At this point, the last available MMSE score was from week 24.

MRI findings of ARIA observed at screening and during the double-blind treatment period of the study are presented below.



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713 Abbreviations: 3-SSAE, 3-point Severity Scale of ARIA-E; APOE, apolipoprotein E; ARIA-E, amyloid-related imaging abnormalities

714 – edema; ARIA-H, amyloid-related imaging abnormalities – hemosiderosis; BGTS, Barkhof Grand Total Scale; CEN, central region;

715 CNS, central nervous system; FRO, frontal lobe; INF, infratentorial region – on each side of the brain; L, left hemisphere; LH,

leptomeningeal hemosiderosis; MB, microbleed; MRI, magnetic resonance imaging; OCC, occipital lobe; PAR, parietal lobe; R, right hemisphere; TEM, temporal lobe; WML, white matter lesion.

Individual-level ARIA map. The overall radiological severity of ARIA-E is given by the BGTS, which can take values between 0 and 60 and is obtained by summing the highest regional ARIA-E scores across 12 brain regions (FRO, TEM, PAR, OCC, CEN, INF, L, R). The regional ARIA-E scores can take values between 0 and 5. The radiological severity of ARIA-E is rated also with the 3-SSAE The radiological severity of ARIA-H is assessed across the same 12 brain regions as ARIA-E and is given by “ARIA-H [count],” the total cumulative number of brain bleeds, which can be of two types, eg, MB and LH. “ARIA-H [count]” at a given MRI visit is the sum between the number of new ARIA-H at that visit and old ARIA-H from all previous MRI visits. The square symbols illustrate only the new ARIA-H at a given MRI visit. The increase in the size of symbols represents an increase in magnitude.

Case 9

This 80-year-old White female with prodromal AD had an MMSE score at baseline of 20, was a non-carrier of APOE ε4 allele, and had no relevant medical history. The screening MRI had no microhemorrhages or SS, and Fazekas score was 1. She was on memantine. She received acetylsalicylic acid 100 mg QD. She was not on anticoagulants.

Her most recent post-baseline MMSE score, at week 24, was 23. The most recent dose of gantenerumab prior to the serious symptomatic ARIA-E event was administered at week 38 (second target dose of 510 mg Q2W). Five days later, the participant developed confusion, apraxia, and motor aphasia; she was unable to hold any object in her hands, write, or speak, but had preserved comprehension. An unscheduled brain MRI scan showed new ARIA-E (BGTS of 34) with multiple hyperintensities and edema in right frontal, right frontoparietal, right postrolandic, right temporal, left frontoparietal, left parietal, left occipital, and left temporo-polar regions, consistent with the symptoms. It also showed six new microhemorrhages in the bilateral parietal and right frontal regions (cumulative ARIA-H count of 6).

The participant was hospitalized on the same day. The blood and CSF tests showed an increase of proteins but no evidence of a cerebral or other infection. She received treatment with mannitol and dexamethasone (8 mg QD for 5 days, with subsequent tapering over the next approximately 6 weeks). Over the next few days, the confusion and apraxia resolved, although there was ongoing aphasia. A follow-up MRI scan showed a slight decrease of intracranial edema. She was subsequently discharged from the hospital. The aphasia resolved. Owing to the BGTS ≥4, treatment with gantenerumab was suspended.

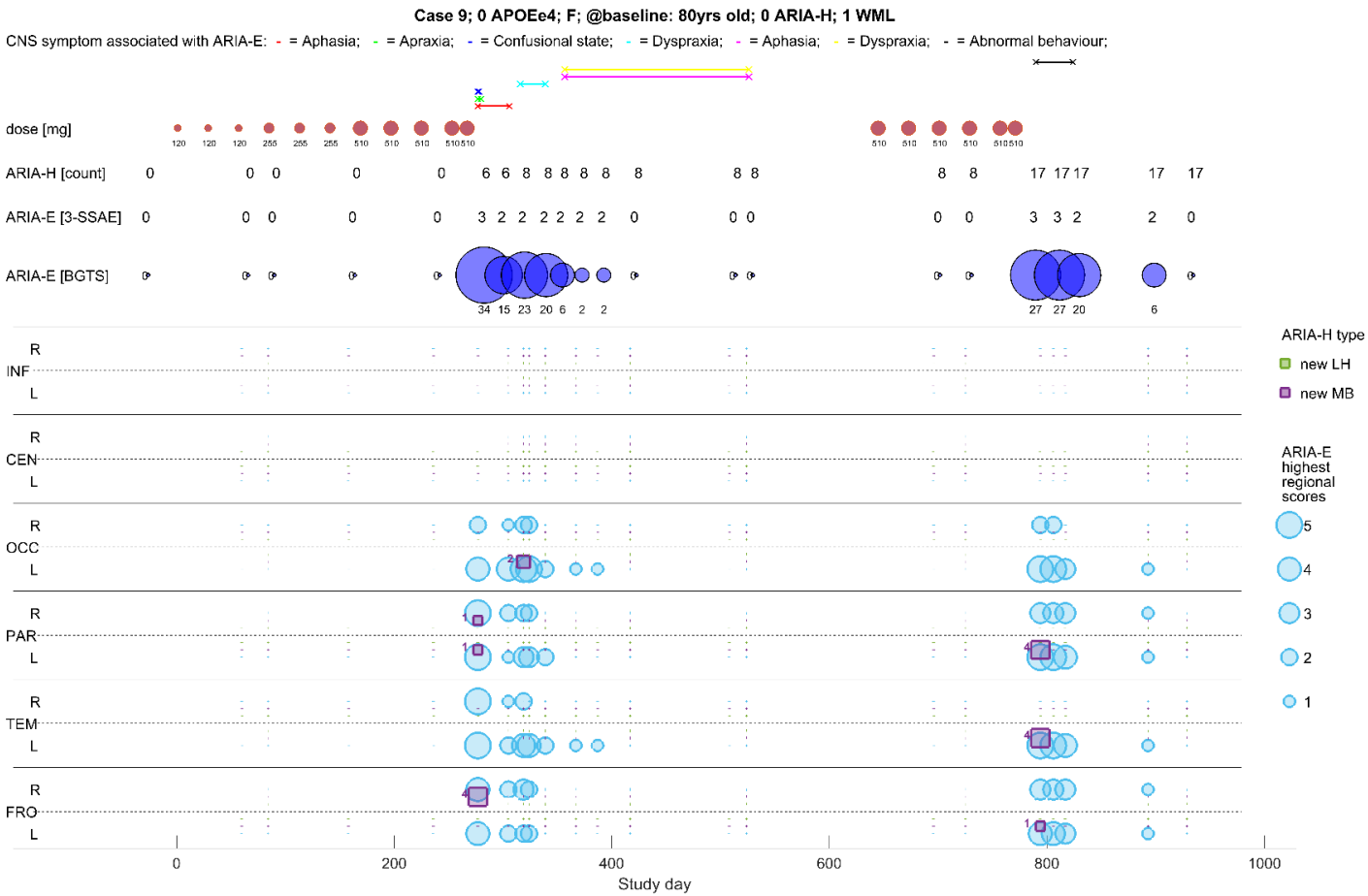
Ten days after hospital discharge, the participant experienced praxis difficulties again and was re-hospitalized for treatment with mannitol and dexamethasone (8 mg QD for 5 days, with subsequent tapering over the following 3 weeks). An unscheduled MRI finding showed two new microhemorrhages in the left occipital region (cumulative ARIA-H of 8). She was discharged 10 days later, after the confusional state and apraxia resolved and the aphasia improved. The aphasia resolved approximately 3 weeks after the hospital discharge. However, 10 days later, the participant had dyspraxia, for which she was again re-hospitalized and treated with mannitol and dexamethasone (8 mg QD for 10 days, with tapering over approximately 4 weeks). She was discharged 10 days after admission after the dyspraxia improved. The dyspraxia resolved 11 days later. However, the participant had a further mild recurrence of aphasia and dyspraxia approximately 3 weeks later.

Approximately 9 weeks after the recurrence of aphasia and dyspraxia, at week 52, MMSE score was 17. A scheduled week 60 MRI scan revealed no ARIA-E findings, but it took approximately 14 weeks for the symptoms to completely resolve. At week 76, MMSE score was 18.

At study week 92, treatment with blinded study drug was resumed. After 6 further gantenerumab doses, including two at target dose level (510 mg Q2W), the participant developed irritability and occasional agitation, and an unscheduled MRI scan showed new ARIA-E (BGTS of 27) in the bilateral frontal, bilateral parietal, bilateral occipital, and left temporal regions. It also showed nine new microhemorrhages in the left frontal, left parietal, and left temporal regions (cumulative ARIA-H of 17, which led to permanent study drug discontinuation as required per the study protocol). The participant was hospitalized and received treatment with mannitol and dexamethasone

(4 mg QD for 1 day, then 8 mg QD for 5 days with tapering over 3 weeks) and was discharged after 4 days. Symptoms resolved over approximately 4 weeks. After 15 weeks, an MRI scan revealed no ARIA-E findings. Her last measured MMSE score, at the early termination visit 118 weeks from baseline, was 15 (5 points lower than at baseline).

MRI findings of ARIA observed during the double-blind treatment period of the study are presented below.



780

781 Abbreviations: 3-SSAE, 3-point Severity Scale of ARIA-E; APOE, apolipoprotein E; ARIA-E, amyloid-related imaging abnormalities

782 – edema; ARIA-H, amyloid-related imaging abnormalities – hemosiderosis; BGTS, Barkhof Grand Total Scale; CEN, central region;

783 CNS, central nervous system; FRO, frontal lobe; INF, infratentorial region – on each side of the brain; L, left hemisphere; LH,

leptomeningeal hemosiderosis; MB, microbleed; MRI, magnetic resonance imaging; OCC, occipital lobe; PAR, parietal lobe; R, right hemisphere; TEM, temporal lobe; WML, white matter lesion.

Individual-level ARIA map. The overall radiological severity of ARIA-E is given by the BGTS, which can take values between 0 and 60 and is obtained by summing the highest regional ARIA-E scores across 12 brain regions (FRO, TEM, PAR, OCC, CEN, INF, L, R). The regional ARIA-E scores can take values between 0 and 5. The radiological severity of ARIA-E is rated also with the 3-SSAE The radiological severity of ARIA-H is assessed across the same 12 brain regions as ARIA-E and is given by “ARIA-H [count],” the total cumulative number of brain bleeds, which can be of two types, eg, MB and LH. “ARIA-H [count]” at a given MRI visit is the sum between the number of new ARIA-H at that visit and old ARIA-H from all previous MRI visits. The square symbols illustrate only the new ARIA-H at a given MRI visit. The increase in the size of symbols represents an increase in magnitude.

Case 10

This 74-year-old White female with prodromal AD had an MMSE score at baseline of 25, was a homozygous APOE ε4 carrier, and had a history of migraines. The screening MRI had no microhemorrhages or SS, and Fazekas score was 1. She was not on symptomatic AD medication. She was on acetylsalicylic acid 81 mg QD. She was not on anticoagulants.

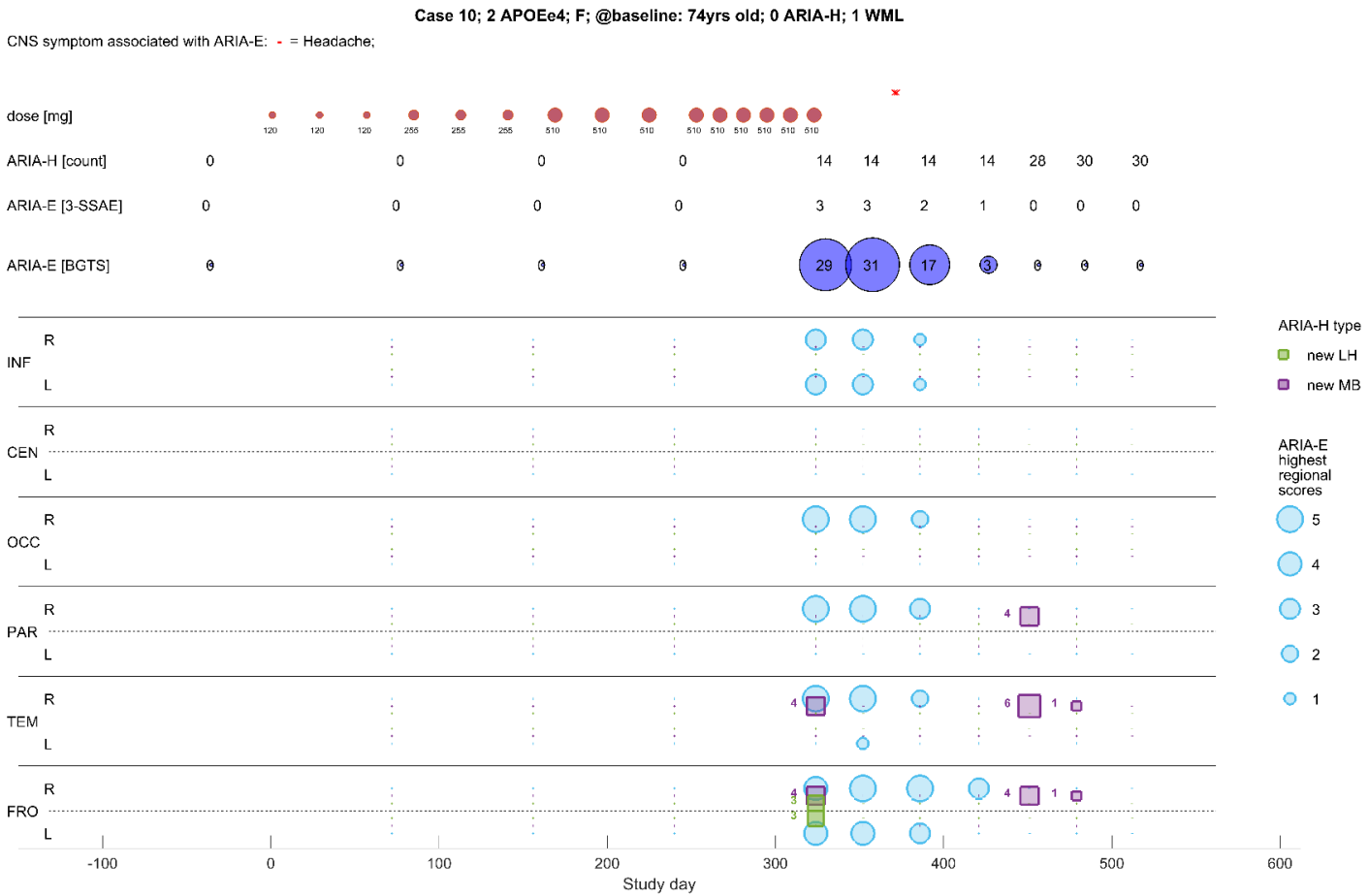
Her most recent post-baseline MMSE score, at week 24, was 24. The most recent dose of gantenerumab prior to the serious symptomatic ARIA-E event was administered at week 46 (sixth target dose of 510 mg Q2W). One day later, the scheduled week 48 MRI scan showed new ARIA-E (BGTS of 29) in the bilateral frontal, bilateral infratentorial, right temporal, right occipital, and right parietal regions. It also revealed eight new microhemorrhages (four in the right frontal and four in the right temporal regions) and six new areas of SS in the bilateral frontal regions (cumulative ARIA-H count of 14; see Figure 2 below for the ARIA-H and the ARIA-E at its highest severity, BGTS of 31, reported on a follow-up MRI). The findings were considered medically significant (ie, serious AEs).

Owing to the week 48 ARIA-H findings of six focal areas of SS cumulatively, treatment with gantenerumab was permanently discontinued as required per the study protocol. While the ARIA-E was ongoing (approximately 7 weeks after its detection), the participant experienced a mild headache treated with paracetamol that resolved within a day.

After approximately 18 weeks from ARIA-E onset, an MRI scan showed that the ARIA-E resolved but it also showed 14 new microhemorrhages in the right frontal, right parietal, and right temporal regions (cumulative ARIA-H of 28). A further MRI scan

4 weeks later showed two new microhemorrhages in the right frontal and right temporal regions (cumulative ARIA-H of 30). Her last measured MMSE score, at an early termination visit 104 weeks from baseline, was 25 (unchanged since baseline).

MRI findings of ARIA observed during the double-blind treatment period of the study are presented below.



822

823 Abbreviations: 3-SSAE, 3-point Severity Scale of ARIA-E; APOE, apolipoprotein E; ARIA-E, amyloid-related imaging abnormalities

824 – edema; ARIA-H, amyloid-related imaging abnormalities – hemosiderosis; BGTS, Barkhof Grand Total Scale; CEN, central region;

825 CNS, central nervous system; FRO, frontal lobe; INF, infratentorial region – on each side of the brain; L, left hemisphere; LH,

826 leptomeningeal hemosiderosis; MB, microbleed; MRI, magnetic resonance imaging; OCC, occipital lobe; PAR, parietal lobe; R,
827 right hemisphere; TEM, temporal lobe; WML, white matter lesion.
828 Individual-level ARIA map. The overall radiological severity of ARIA-E is given by the BGTS, which can take values between 0 and
829 60 and is obtained by summing the highest regional ARIA-E scores across 12 brain regions (FRO, TEM, PAR, OCC, CEN, INF, L,
830 R). The regional ARIA-E scores can take values between 0 and 5. The radiological severity of ARIA-E is rated also with the 3-
831 SSAE The radiological severity of ARIA-H is assessed across the same 12 brain regions as ARIA-E and is given by “ARIA-H
832 [count],” the total cumulative number of brain bleeds, which can be of two types, eg, MB and LH. “ARIA-H [count]” at a given MRI
833 visit is the sum between the number of new ARIA-H at that visit and old ARIA-H from all previous MRI visits. The square symbols
834 illustrate only the new ARIA-H at a given MRI visit. The increase in the size of symbols represents an increase in magnitude.

Case 11

This 73-year-old White female with prodromal AD had an MMSE score at baseline of 22, was a homozygous APOE ε4 carrier, and had no relevant medical history. The screening MRI had no microhemorrhages or SS, and Fazekas score was 1. The participant was not on symptomatic AD medication, antiplatelets, or anticoagulants.

Prior to the serious symptomatic ARIA-E event, the participant had an asymptomatic ARIA-E episode from study week 44 to week 64, after three doses of 510 mg Q4W gantenerumab, with a maximum BGTS severity of 15 and dosing suspension. She also concurrently had nine new microhemorrhages in the bilateral temporal region and one new focal area of SS in the left temporal region at week 48 (cumulative ARIA-H of 11).

Following gantenerumab dosing resumption, 11 gantenerumab doses, including 10 target doses (510 mg Q2W) were administered. Her MMSE score at week 76 was 22. At week 86, within hours of the tenth target gantenerumab dose, the participant developed a strange facial appearance and profound speech disturbance. She also had comprehension difficulties. She presented to the emergency room where she was noted to have increased blinking frequency and subtle, symmetrical perioral contractions, high flicker frequency, symmetrical facial grimace, and conjugated gaze with a tendency to look towards the right. The bilateral flexor response was present and symmetrical. She was able to maintain all four extremities against gravity, with occasional claudication and clonus. She was diagnosed with moderate events of aphasia and status epilepticus. It was reported that she also had an “evening headache” for approximately 3 weeks. A local cranial CT scan with angiography

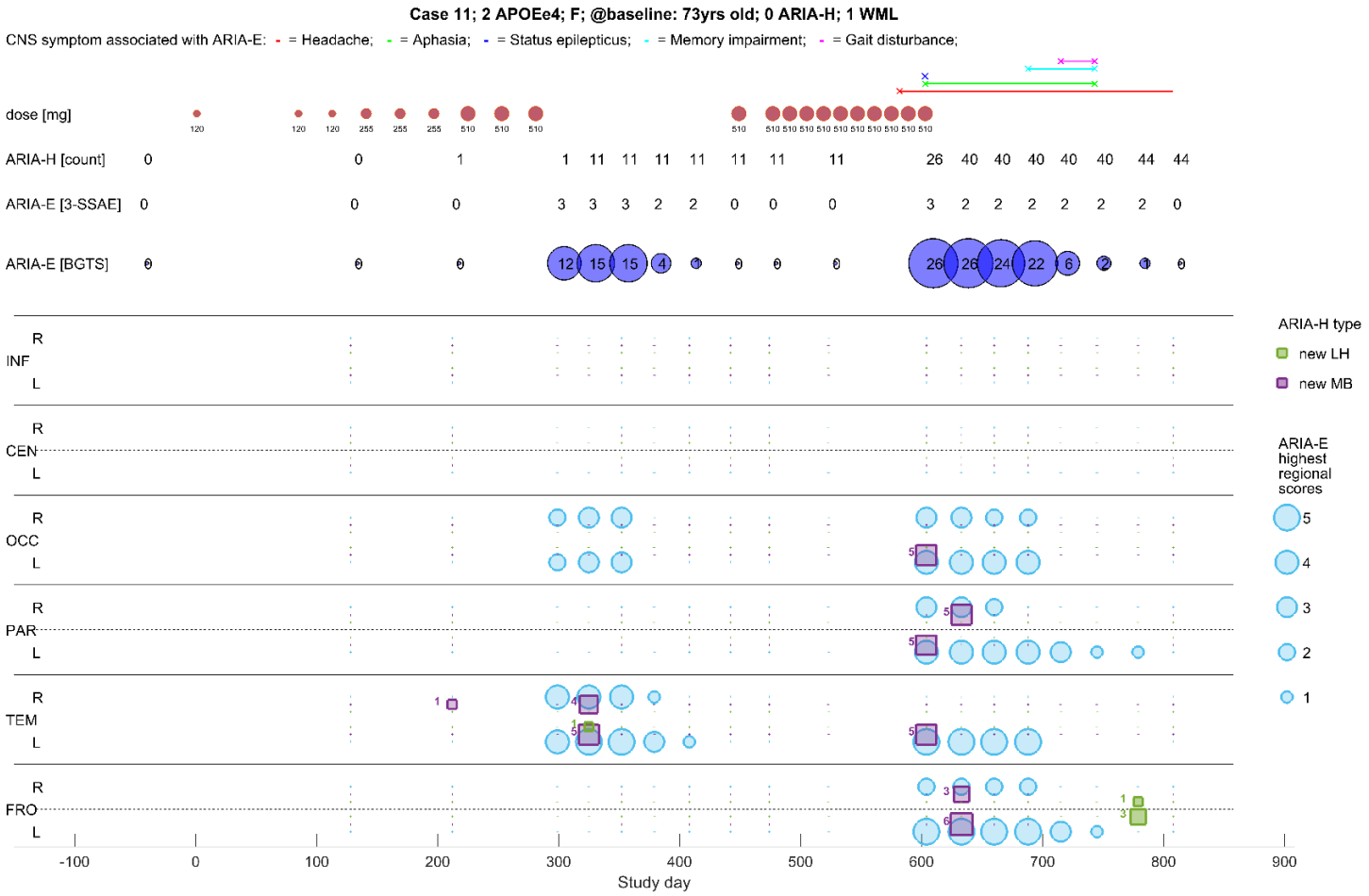
showed vasogenic edema with extensive hypodensities of white matter mainly affecting left hemisphere (temporal, frontal, and parietal lobe), with less intensity in the right hemisphere (posterior regions); no large vessel occlusion was noted. Locally performed MRI showed areas of bi-hemispheric vasogenic edema (predominantly left with cortical involvement) associated with multiple microhemorrhages. The hemogram and biochemistry results were normal. She was diagnosed with ARIA-E of severe intensity and hospitalized. She received treatment with methylprednisolone (1 g QDfor 5 days), and levetiracetam (starting dose of 3 g QD, tapered over 22 weeks). The status epilepticus resolved the same day with treatment.

An MRI scan the next day confirmed ARIA-E findings (BGTS of 26) in the left temporal, bilateral frontal, bilateral parietal, and bilateral occipital regions. It also showed 15 new microhemorrhages in the left parietal, left occipital, and left temporal regions (cumulative ARIA-H of 26, leading to permanent study drug discontinuation as required per the study protocol; see Figure 3 below).

On the same day, an EEG showed slow and attenuated periodic epileptiform activity in the left hemisphere, suggestive of lesional interictal pericritic pattern. An EEG repeated after 9 days showed that periodic activity persisted but with significant improvement and the participant was discharged from the hospital on lacosamide (300 mg QD) with close follow-up. Three weeks later, MRI showed 14 new microhemorrhages in the bilateral frontal and right parietal regions (cumulative ARIA-H count of 40). She subsequently attended an early termination visit and had an MMSE score of 14. Approximately 6 weeks later, the participant was noted to have worsening memory problems (of mild severity). Approximately 4 weeks after that, she experienced mild gait disturbance. A further 4 weeks later, the aphasia, memory

impairment, and gait disturbance were considered resolved. Approximately 5 weeks later, MRI showed four new areas of SS in the bilateral frontal region (cumulative ARIA-H count of 44). After a further 4 weeks, MRI revealed no ARIA-E. Approximately 13 weeks later, the participant was reported to be stable, with right hemicranial headache about 5–10 days a month, which subsided with paracetamol treatment. The headache was resolving at the time of study completion. Her last measured MMSE score, at week 116, was 20 (2 points lower than baseline, but 6 points higher than at the early termination visit).

MRI findings of ARIA observed during the double-blind treatment period of the study are presented below.



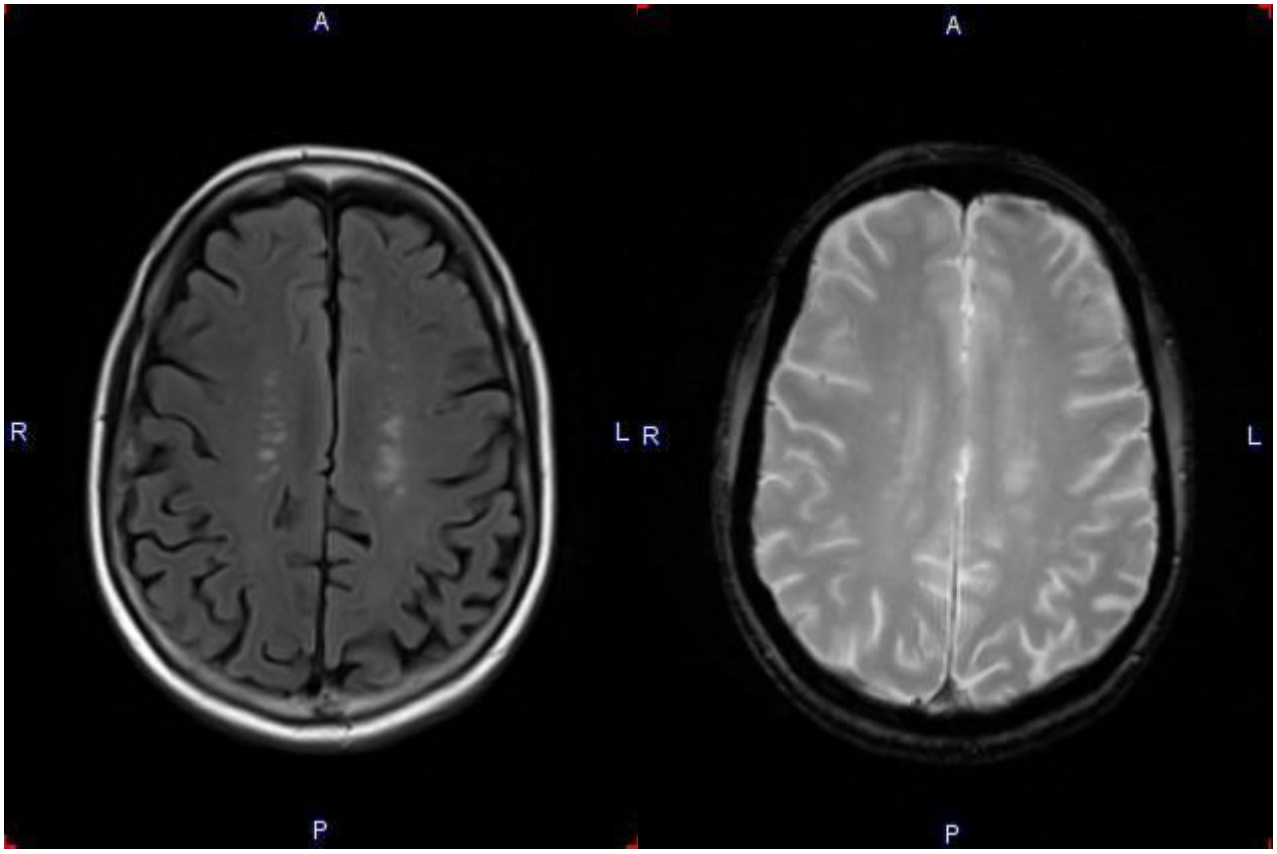
893

894 Abbreviations: 3-SSAE, 3-point Severity Scale of ARIA-E; APOE, apolipoprotein E; ARIA-E, amyloid-related imaging abnormalities

895 – edema; ARIA-H, amyloid-related imaging abnormalities – hemosiderosis; BGTS, Barkhof Grand Total Scale; CEN, central region;

CNS, central nervous system; FRO, frontal lobe; INF, infratentorial region – on each side of the brain; L, left hemisphere; LH, leptomeningeal hemosiderosis; MB, microbleed; MRI, magnetic resonance imaging; OCC, occipital lobe; PAR, parietal lobe; R, right hemisphere; TEM, temporal lobe; WML, white matter lesion.

Individual-level ARIA map. The overall radiological severity of ARIA-E is given by the BGTS, which can take values between 0 and 60 and is obtained by summing the highest regional ARIA-E scores across 12 brain regions (FRO, TEM, PAR, OCC, CEN, INF, L, R). The regional ARIA-E scores can take values between 0 and 5. The radiological severity of ARIA-E is rated also with the 3-SSAE The radiological severity of ARIA-H is assessed across the same 12 brain regions as ARIA-E and is given by "ARIA-H [count]," the total cumulative number of brain bleeds, which can be of two types, eg, MB and LH. "ARIA-H [count]" at a given MRI visit is the sum between the number of new ARIA-H at that visit and old ARIA-H from all previous MRI visits. The square symbols illustrate only the new ARIA-H at a given MRI visit. The increase in the size of symbols represents an increase in magnitude.



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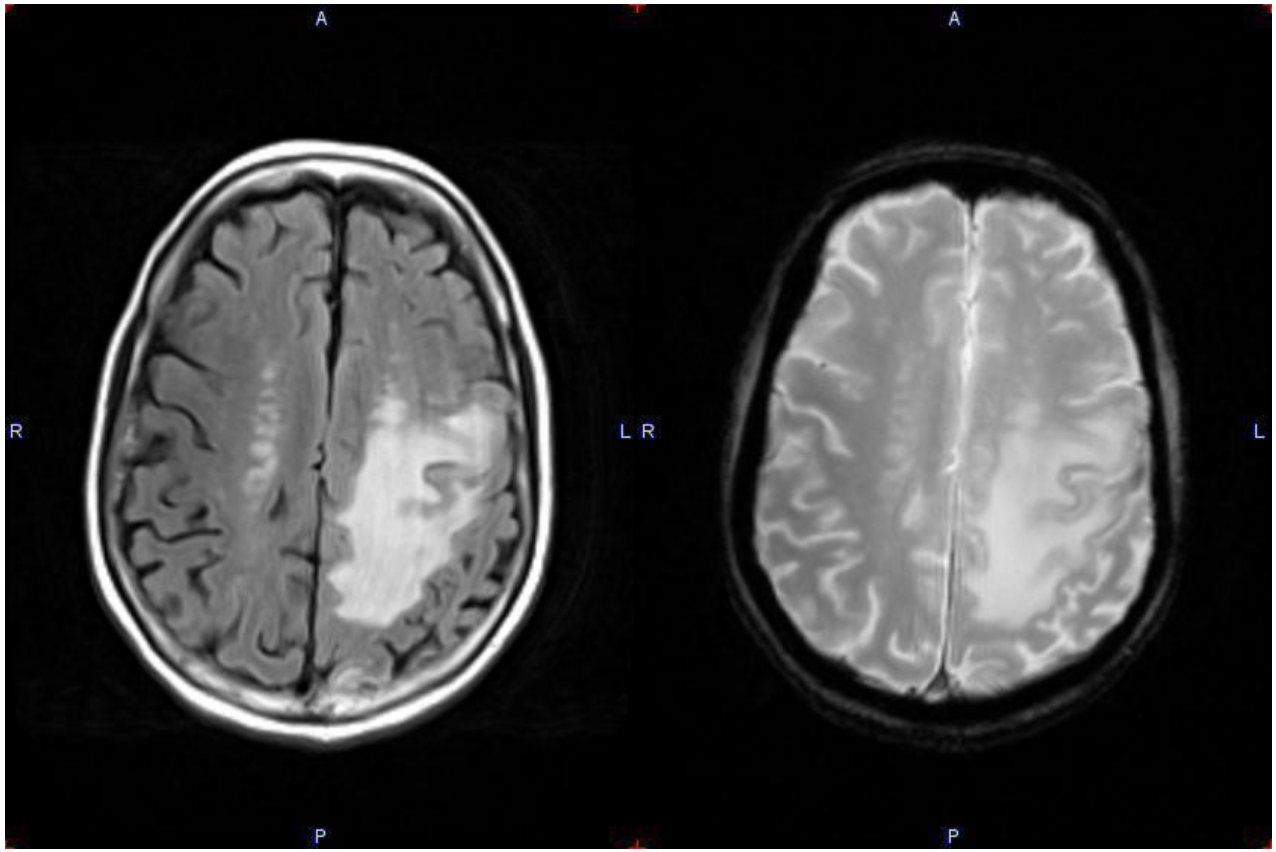

Figure 1 (Case 1). Upper: FLAIR (left) and T2*-weighted (right) sequences at baseline. **Lower:** Representative image shows ARIA-E in the left frontal, parietal, and occipital regions on a FLAIR sequence; BGTS of 11 (left). No concurrent new ARIA-H on a T2*-weighted sequence (right). The participant experienced right-sided weakness, dysarthria, and dizziness. The ARIA-E was ongoing per the last available MRI.

912 Abbreviations: ARIA-E, amyloid-related imaging abnormalities – edema; ARIA-H, amyloid-related imaging abnormalities –

913 hemosiderosis; BGTS, Barkhof Grand Total Scale; FLAIR, fluid-attenuated inversion recovery; MRI, magnetic resonance imaging.

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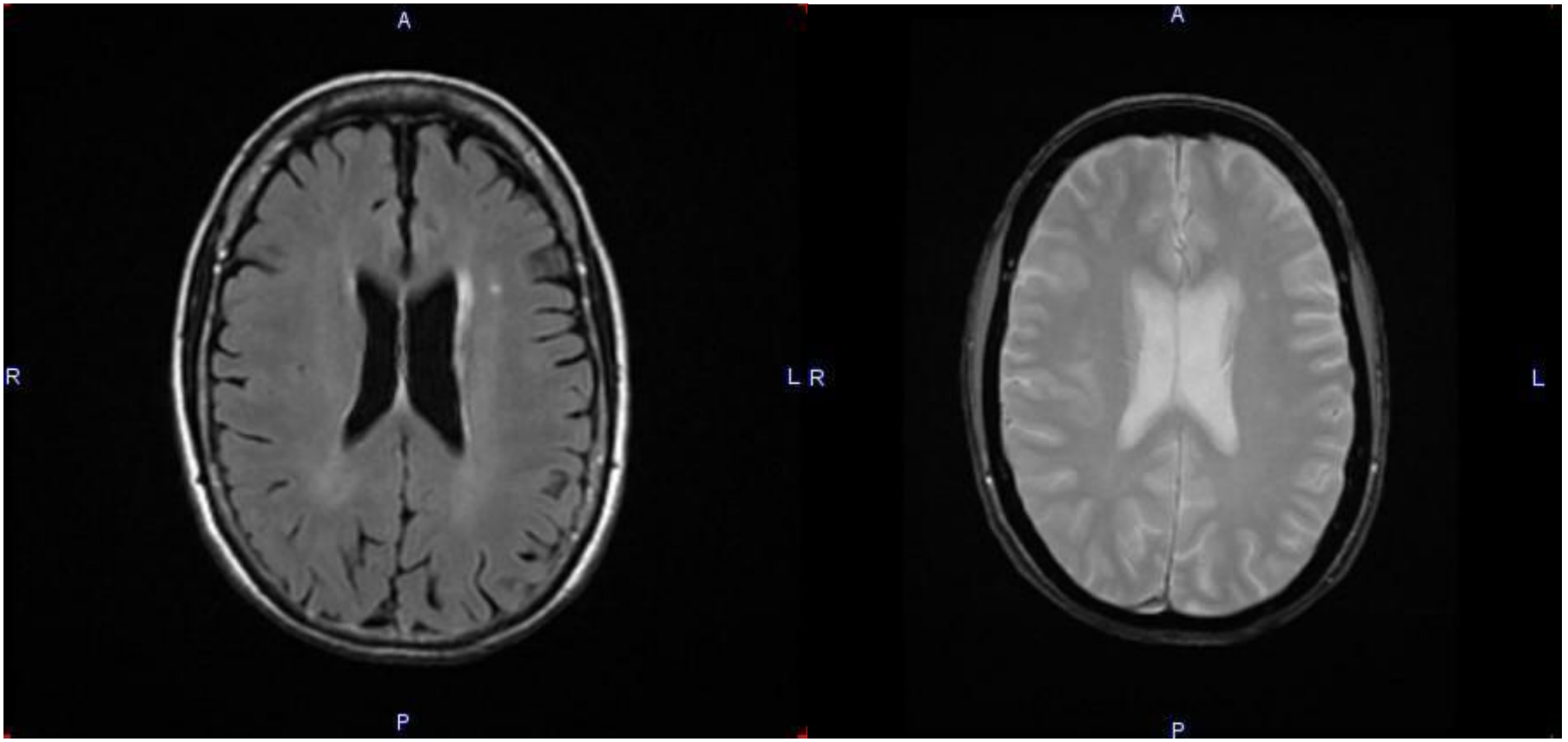

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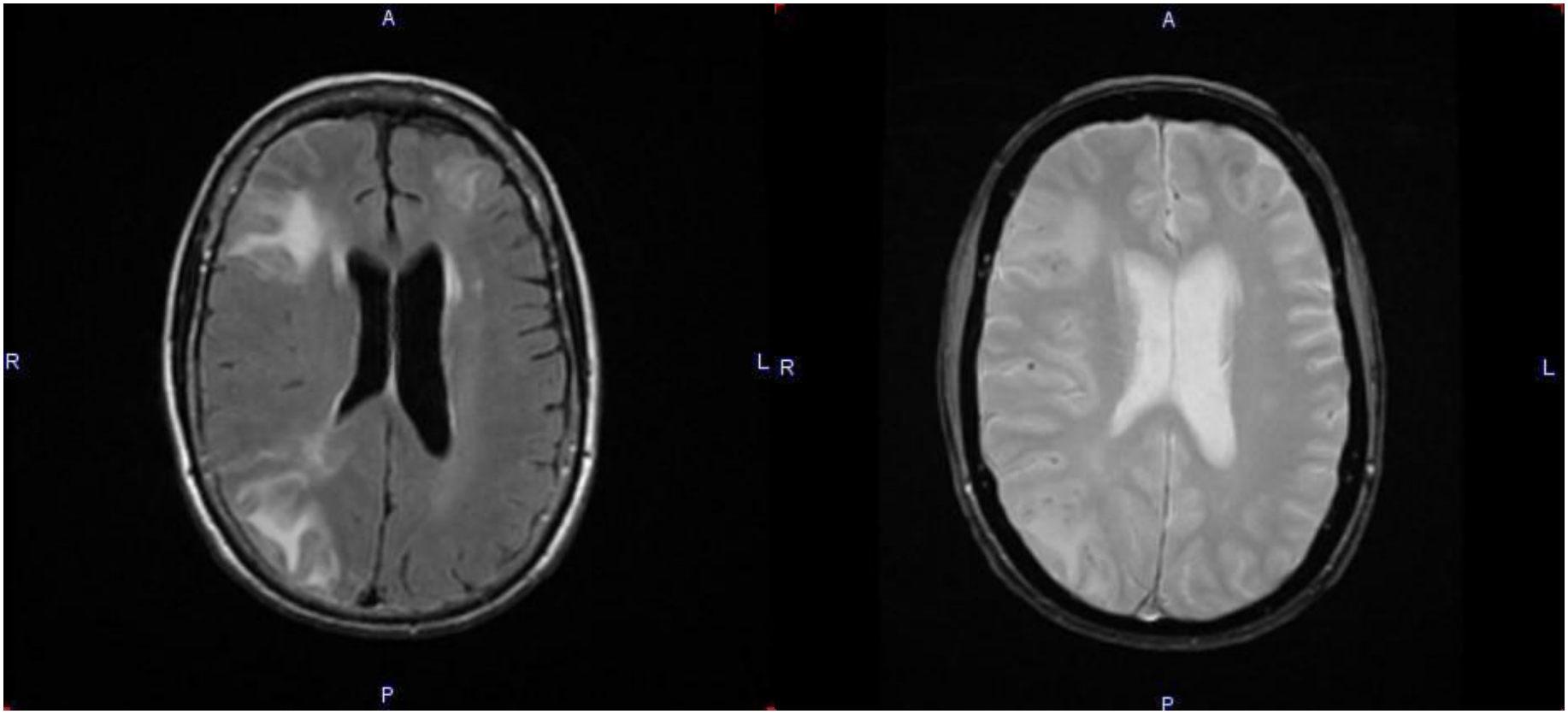

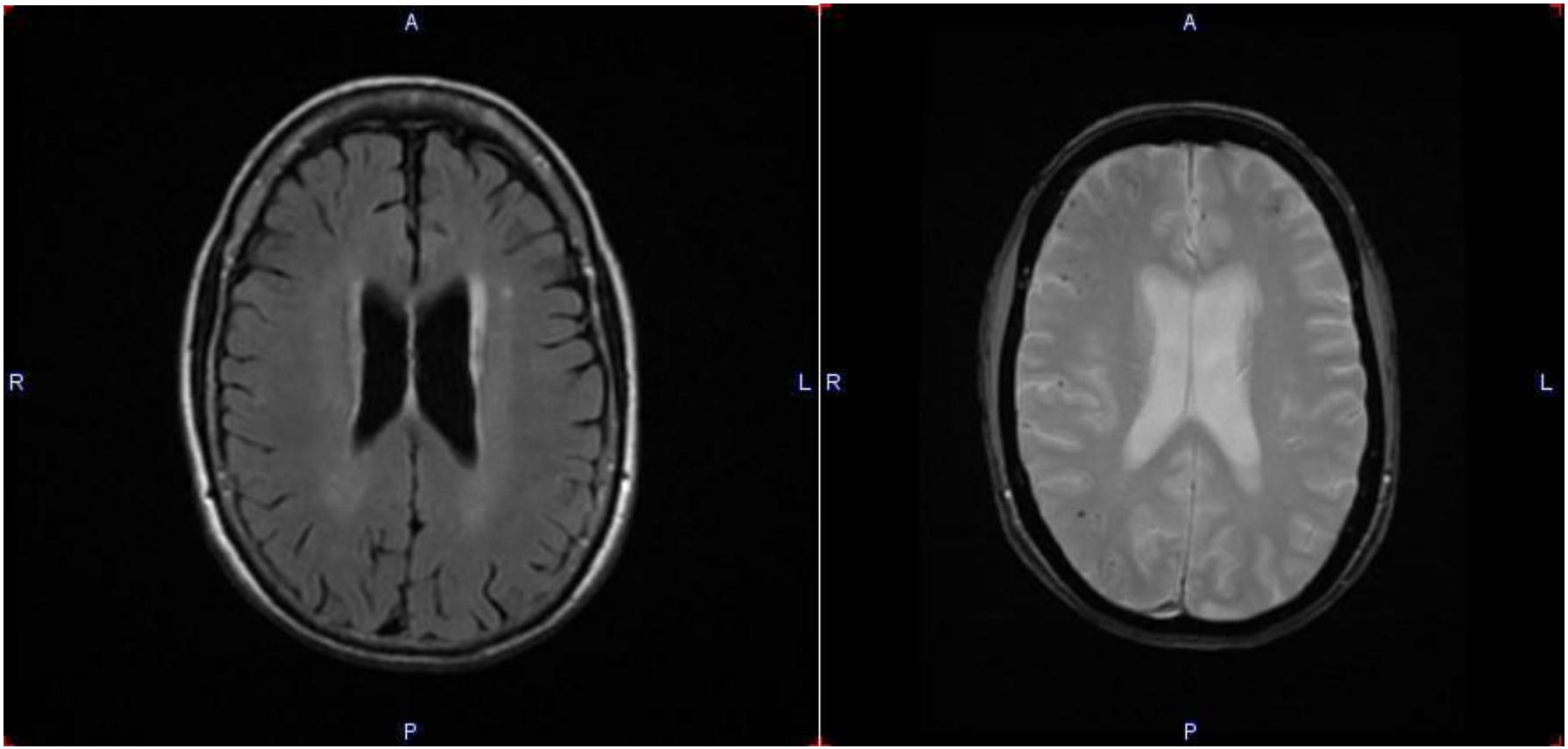

Figure 2 (Case 10). Upper: FLAIR (left) and T2*-weighted (right) sequences at baseline. **Middle:** Representative image shows frontal ARIA-E bilaterally, and in the right parieto-occipital regions on a FLAIR sequence, BGTS of 31 (left); concurrent new ARIA-H including four new microhemorrhages in the right fronto-parietal regions and six new areas of SS were detected in the bilateral frontal regions on a T2*-weighted sequence (representative image, right). The participant experienced mild headache for 1 day,

reported approximately 7 weeks after the ARIA-E detection. **Lower:** FLAIR (left) and T2*-weighted (right) MRI sequences at the time point of ARIA-E resolution.

Abbreviations: ARIA-E, amyloid-related imaging abnormalities – edema; ARIA-H, amyloid-related imaging abnormalities – hemosiderosis; BGTS, Barkhof Grand Total Scale; FLAIR, fluid-attenuated inversion recovery; MRI, magnetic resonance imaging.

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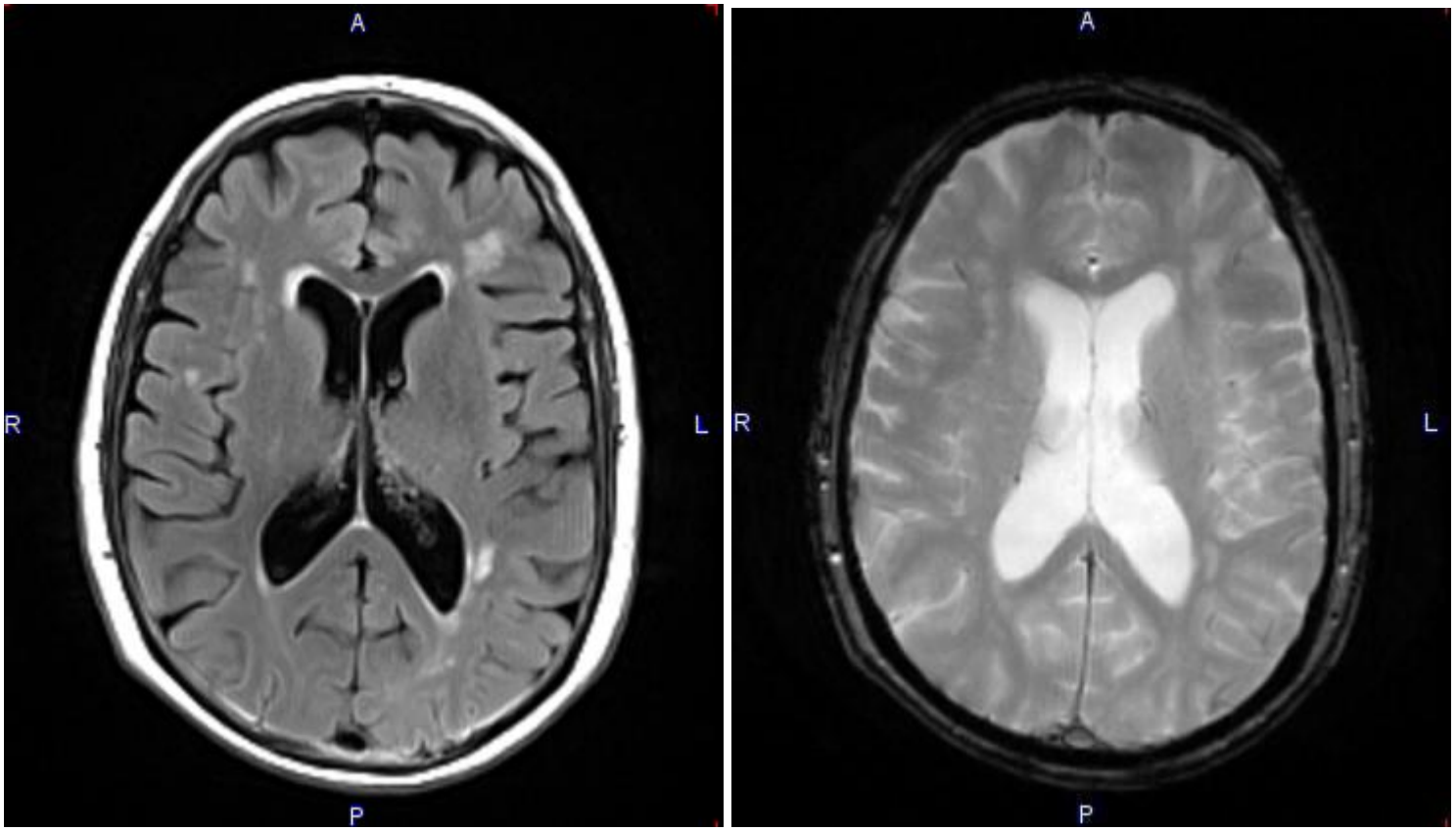

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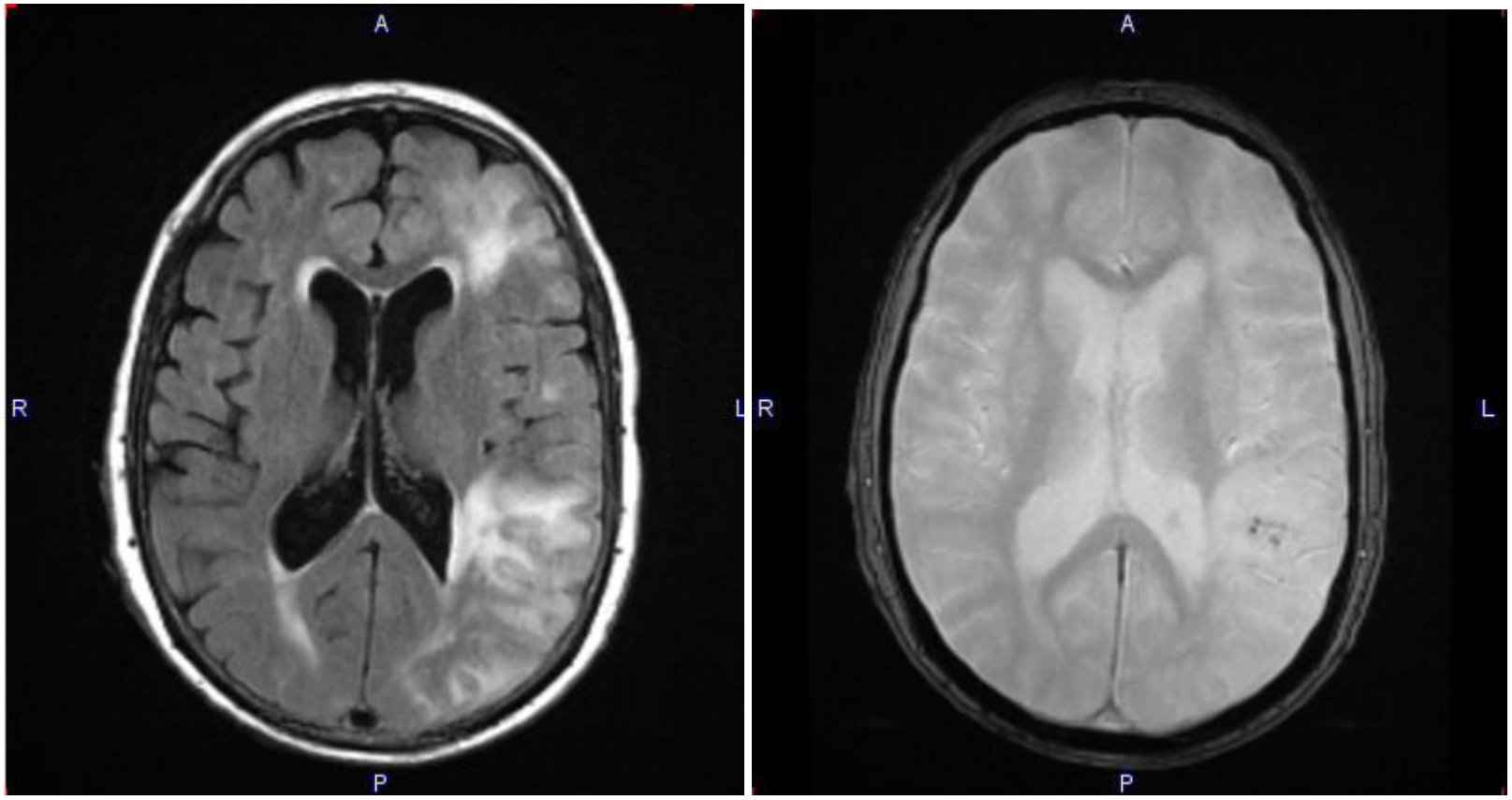

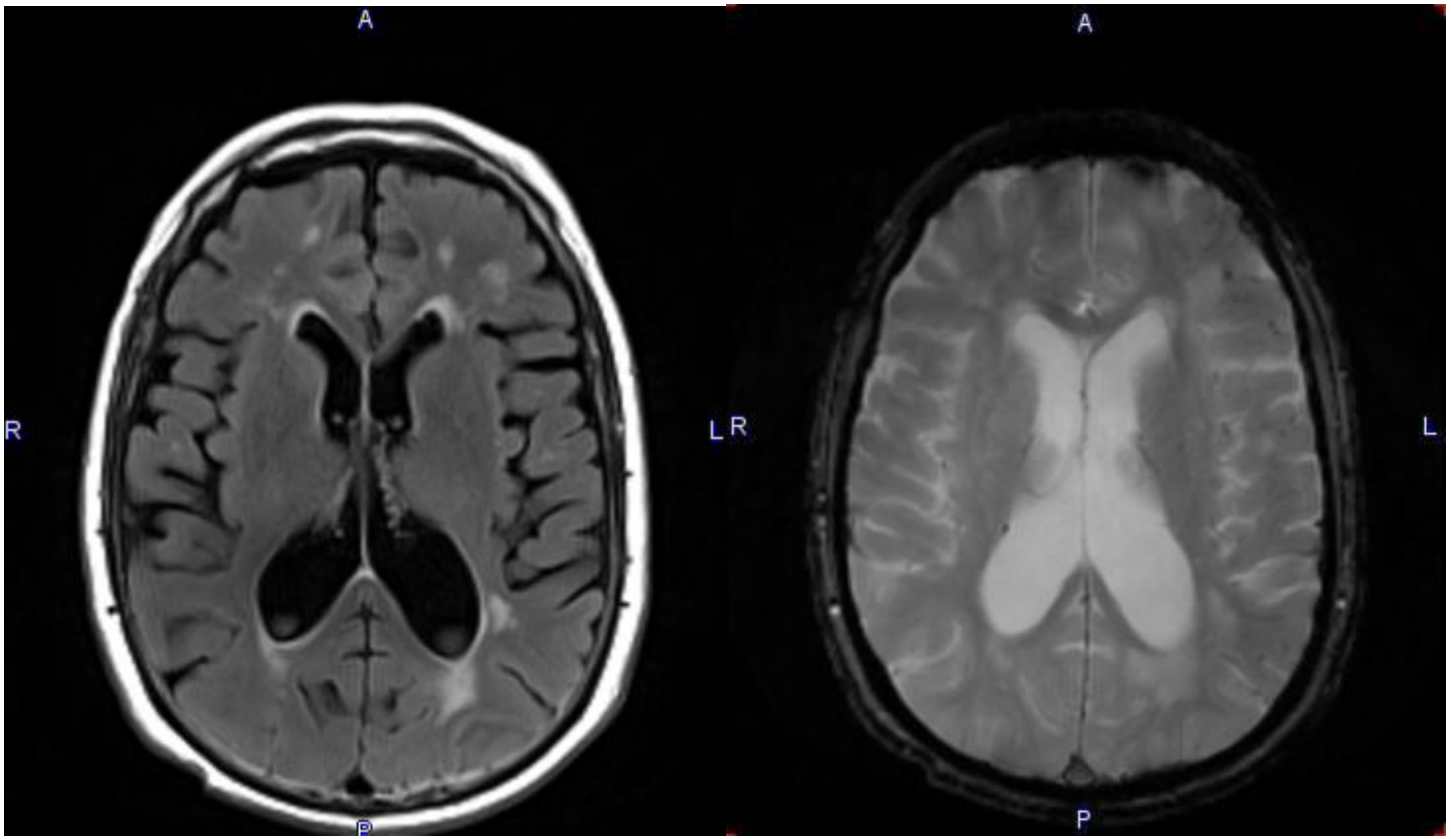

Figure 3 (Case 11). Upper: FLAIR (left) and T2*-weighted (right) sequences at baseline. **Middle:** Representative image shows ARIA-E in the bilateral parietal and occipital regions and left temporal and frontal regions on a FLAIR sequence, BGTS of 26 (left); concurrent new ARIA-H (15 new microhemorrhages in the left parietal, occipital, and temporal regions; cumulative ARIA-H of 26) were detected on a T2*-weighted sequence (representative image, right). The participant experienced headache, status

epilepticus, aphasia, memory impairment, and gait disturbance. **Lower:** FLAIR (left) and T2*-weighted (right) MRI sequences at the time point of ARIA-E resolution.

Abbreviations: ARIA-E, amyloid-related imaging abnormalities – edema; ARIA-H, amyloid-related imaging abnormalities – hemosiderosis; BGTS, Barkhof Grand Total Scale; FLAIR, fluid-attenuated inversion recovery; MRI, magnetic resonance imaging.

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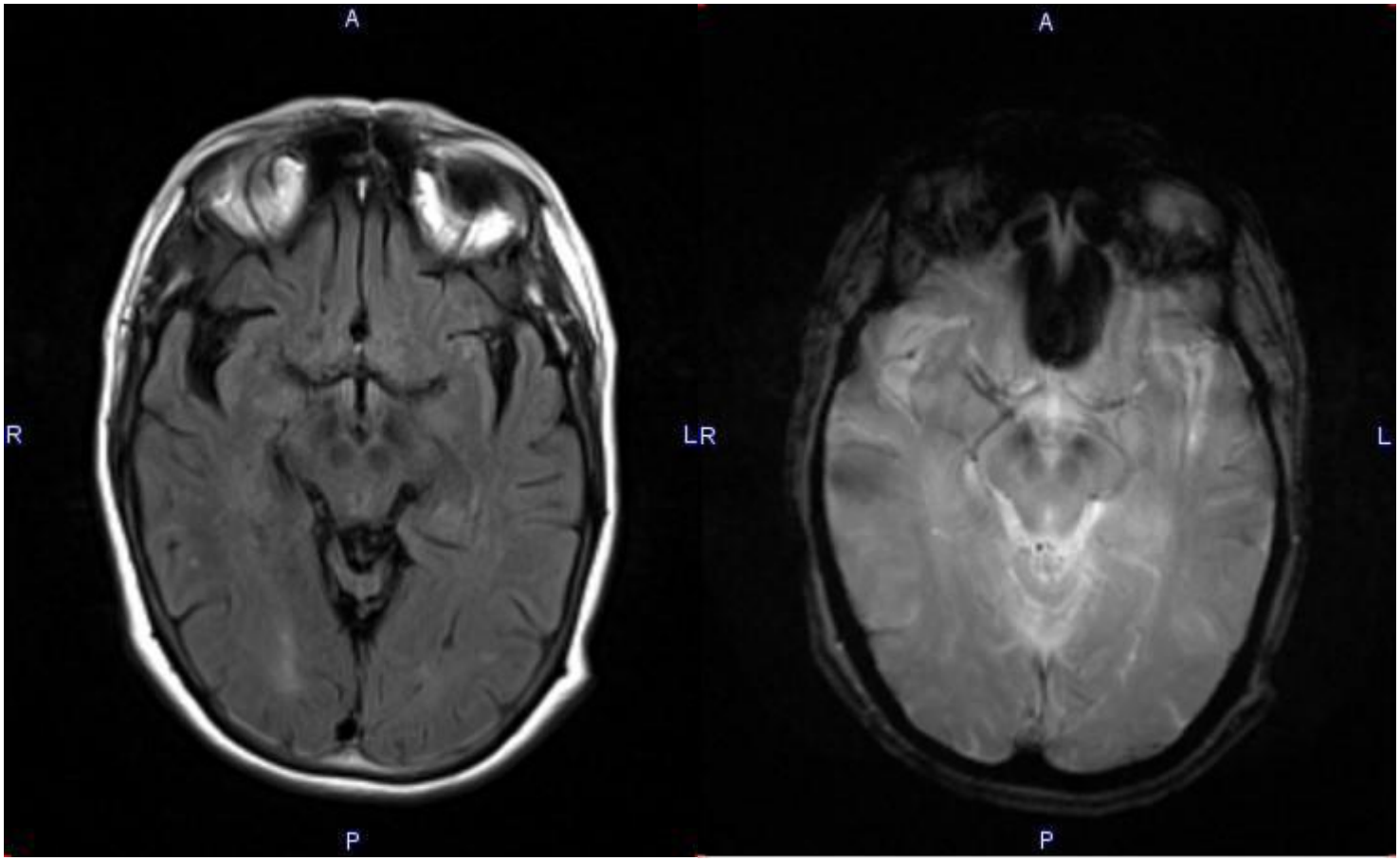

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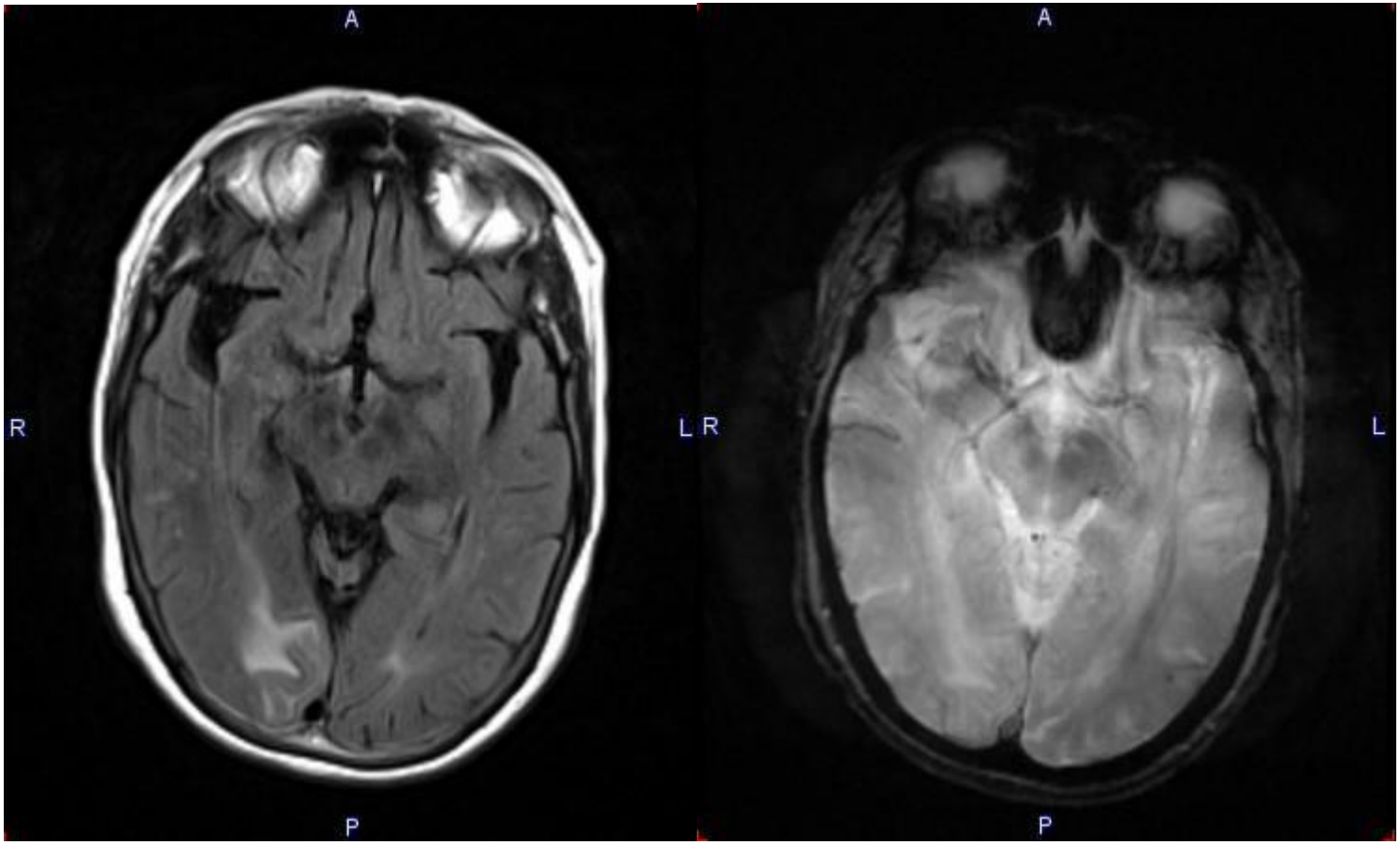

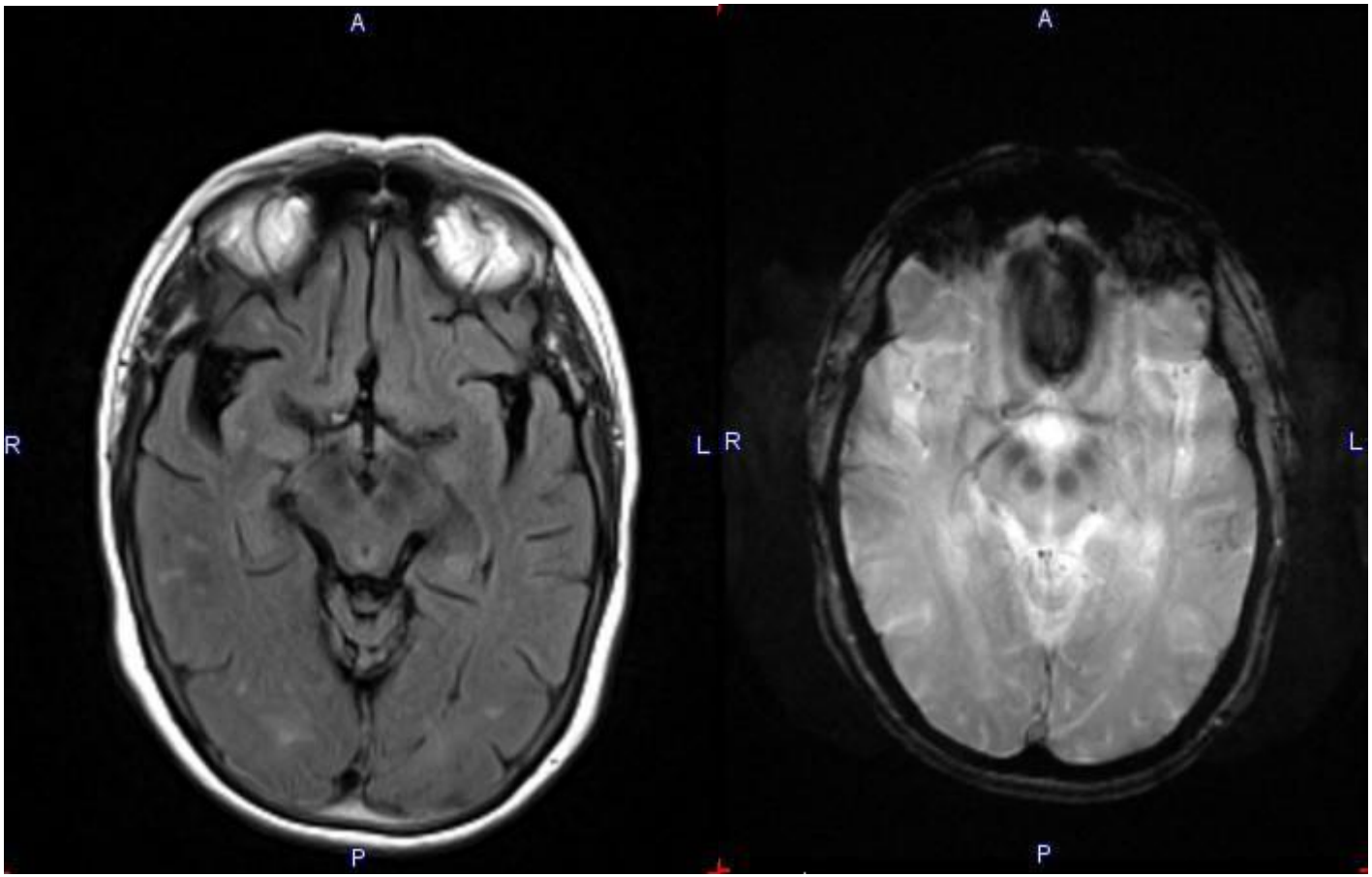

Figure 4 (Case 4). Upper: FLAIR (left) and T2*-weighted (right) sequences at baseline. **Middle:** Representative image shows ARIA-E in the right occipital region on a FLAIR sequence; BGTS of 3 (left). No concurrent new ARIA-H on a T2*-weighted sequence (right). The participant experienced vestibular dysfunction considered to be related by the PI to blinded study drug and

ear lavage for excessive cerumen. **Lower:** FLAIR (left) and T2*-weighted (right) MRI sequences at the time point of ARIA-E resolution.

Abbreviations: ARIA-E, amyloid-related imaging abnormalities – edema; ARIA-H, amyloid-related imaging abnormalities – hemosiderosis; BGTS, Barkhof Grand Total Scale; FLAIR, fluid-attenuated inversion recovery; MRI, magnetic resonance imaging; PI, principal investigator.

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