Biomarker pattern of ARIA-E participants in phase 3 randomized clinical trials with bapineuzumab

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Abstract

Objective
To evaluate whether amyloid-related imaging abnormalities with edema/effusion (ARIA-E) observed in bapineuzumab clinical trials was associated with specific biomarker patterns.

Methods
Bapineuzumab, an anti-β-amyloid monoclonal antibody, was evaluated in patients with mild to moderate Alzheimer disease. Amyloid PET imaging, CSF biomarkers, or volumetric MRI (vMRI) were assessed.

Results
A total of 1,512 participants underwent one or more biomarker assessments; 154 developed incident ARIA-E. No differences were observed at baseline between ARIA-E and non-ARIA-E participants in brain amyloid burden by PET, the majority of vMRI measures, or CSF biomarkers, with the exception of lower baseline CSF Aβ42 in APOE ε4 noncarrier ARIA-E vs non-ARIA-E groups (bapineuzumab non-ARIA-E p = 0.027; placebo non-ARIA-E p = 0.012). At week 71, bapineuzumab-treated participants with ARIA-E vs non-ARIA-E showed greater reduction in brain amyloid PET, greater reductions in CSF phosphorylated tau (p-tau) (all comparisons p < 0.01), and total tau (t-tau) (all comparisons p < 0.025), and greater hippocampal volume reduction and ventricular enlargement (all p < 0.05). Greater reduction in CSF Aβ40 concentrations was observed for ARIA-E versus both non-ARIA-E groups (bapineuzumab/placebo non-ARIA-E p = 0.015/0.049). No group differences were observed at week 71 for changes in whole brain volume or CSF Aβ42.

Conclusions
Baseline biomarkers largely do not predict risk for developing ARIA-E. ARIA-E was associated with significant longitudinal changes in several biomarkers, with larger reductions in amyloid PET and CSF p-tau and t-tau concentrations, and paradoxically greater hippocampal volume reduction and ventricular enlargement, suggesting that ARIA-E in bapineuzumab-treated cases may be related to increased Aβ efflux from the brain and affecting downstream pathogenic processes.
An urgent international priority is the search for effective therapies for Alzheimer disease (AD). Major efforts have been directed at developing disease-modifying therapies targeting β-amyloid (Aβ) aggregation and toxicity, believed to initiate the cascade of events that lead to the disease. The search so far has been unsuccessful; but insights from these efforts have helped refine clinical trial methodology.

Observations of MRI abnormalities in trials evaluating anti-amyloid therapies for AD led to the use of the term amyloid-related imaging abnormalities (ARIA) to describe a spectrum of MRI findings. ARIA-E refers to areas of hyperintensity on fluid-attenuation inversion recovery (FLAIR) MRI reflecting parenchymal edema or sulcal effusion and ARIA-H refers to areas of hypointensity on T2*‐weighted gradient echo MRI reflecting iron deposits in the form of hemosiderin. Animal models indicate that anti-Aβ treatment removes vascular amyloid, resulting in leakage of blood, fluid imbalances, and microhemorrhages/hemosiderin deposition.

Bapineuzumab, an anti-Aβ monoclonal antibody, was evaluated in phase 3 trials for the treatment of mild to moderate AD.

Centralized reviews of bapineuzumab MRI scans have shown increased risk for developing ARIA-E with increasing number of APOE ε4 alleles, with increasing bapineuzumab dose, and in bapineuzumab-treated carriers who had microhemorrhages at baseline. The reported ARIA-E cases were largely asymptomatic and typically resolved without intervention within 90 days of detection. Similar patterns were observed in trials with other anti-Aβ monoclonal antibodies, gantenerumab, and aducanumab.

The objective of this study was to compare the CSF and imaging biomarker pattern between participants who developed ARIA-E and those who did not.

**Methods**

**Patients**

Enrollment and randomization for the bapineuzumab phase 3 Pittsburgh compound B (PiB) PET, CSF, and volumetric MRI (vMRI) substudies were the same as for the main studies described previously. In brief, eligible patients were aged 50–88 years inclusive, met clinical criteria for probable AD, had a Mini-Mental State Examination (MMSE) score of 16–26, and had a modified Hachinski Ischemic Score ≤4. A key exclusion was evidence of clinically significant neurologic disease other than AD.

In the APOE ε4 carrier study, 1,121 participants were randomized in a ratio of 3:2 bapineuzumab 0.5 mg/kg to placebo. In the noncarrier study, 1,331 participants were randomized in a ratio of 1:1:1:2 bapineuzumab 0.5 mg/kg:1 mg/kg:2 mg/kg to placebo. The 2 mg/kg dose was discontinued early in the trial owing to safety events (symptomatic ARIA) but participants randomized to that dose were included in these analyses. Stratification factors used in randomization included baseline MMSE total score (low 16 to 21 vs high 22 to 26); current cholinesterase inhibitor or memantine use; and, in the carrier study, APOE ε4 copy number (1 vs 2). Study drug was administered as a 1-hour IV infusion every 13 weeks during the 18-month study.

The primary objective of the phase 3 studies was to evaluate the efficacy of bapineuzumab compared with placebo by measuring the change from baseline to week 78 in cognitive and functional endpoints. Key secondary objectives were to evaluate the effect of bapineuzumab on change from baseline to week 71 in brain Aβ burden by 11C-PiB PET, change in CSF phosphorylated tau (p-tau), and global brain volume reduction in subsets. Exploratory objectives included pooled analyses using all analyzable patients from both studies on the effect of bapineuzumab on 11C-PiB PET, CSF p-tau, and global/regional vMRI changes. Biomarker sample sizes for each of the studies (carriers and noncarriers) were reported previously and are provided in figure e-1 (links.lww.com/WNL/A213).

11C-PiB PET scans were obtained at baseline, week 45, and week 71. PET imaging was conducted at 14 US academic PET centers. Camera-specific acquisition, emission correction, and reconstruction settings were adopted from the Alzheimer’s Disease Neuroimaging Initiative. Image analyses were performed by a core imaging laboratory for 11C-PiB PET signal (standard uptake value ratio [SUVr]) in a global composite average (GCA) comprising 5 cortical brain regions known to accumulate amyloid in AD (anterior cingulate, frontal cortex, lateral temporal cortex, parietal cortex, and posterior cingulate/precuneus) relative to a reference region (cerebellar gray matter). Three-dimensional T1-weighted MRI scans were obtained at screening and weeks 19, 45, and

**Glossary**

Aβ = β-amyloid; AD = Alzheimer disease; ANCOVA = analysis of covariance; ARIA = amyloid-related imaging abnormalities; ARIA-E = amyloid-related imaging abnormalities–edema or effusion; BBSI = brain boundary shift integral; CI = confidence interval; FLAIR = fluid-attenuation inversion recovery; GCA = global composite average; HBSI = hippocampal boundary shift integral; HCV = hippocampal volume; LS = least square; MMSE = Mini-Mental State Examination; p-tau = phosphorylated tau; PiB = Pittsburgh compound B; SUVr = standard uptake value ratio; t-tau = total tau; VBSI = ventricular boundary shift integral; vMRI = volumetric MRI; VV = ventricular volume; WBV = whole brain volume.

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71 for brain vMRI. Changes were measured in whole brain volume (WBV) by the brain boundary shift integral (BBSI), ventricular volume (VV) by the ventricular boundary shift integral (VBSI), and total hippocampal volume (HCV) by hippocampal boundary shift integral (HBSI). Methods for image acquisition, processing, and quantitation were previously described.\textsuperscript{10} CSF samples were collected at baseline and week 71, and Aβ40, Aβ42, p-tau, and total tau (t-tau) concentrations determined. Methods for sample collection, bioanalysis, and quantitation were described in Blennow et al.\textsuperscript{22}

Determination of ARIA-E FLAIR MRI brain images were obtained at the screening visit; weeks 6, 19, 32, 45, 58, and 71; and additionally as necessary per physician’s discretion for safety monitoring. All FLAIR MRI brain images were read retrospectively at the central imaging core laboratory by 2 readers reaching a consensus. ARIA-E was defined as evidence of parenchymal or sulcal hyperintensity.\textsuperscript{8,13}

**Statistical analysis**

Participants who received at least part of one infusion and had at least one satisfactory retrospective safety MRI read were categorized into 3 groups: bapineuzumab-treated participants who developed ARIA-E, bapineuzumab-treated participants who did not develop ARIA-E (bapineuzumab non-ARIA-E), and placebo-treated participants who did not develop ARIA-E (placebo non-ARIA-E). All 3 groups included only patients who had no ARIA-E at baseline. Eight patients in the placebo arm developed incident ARIA-E but were excluded from these analyses since none had \(^{11}\text{C-PiB PET}\) data, only 2 had CSF data, and 3 had vMRI data. Since all ARIA-E participants included in these analyses were bapineuzumab-treated, this group is referred to as ARIA-E participants for simplicity.

Baseline levels of \(^{11}\text{C-PiB PET GCA SUVr}\), CSF p-tau, t-tau, Aβ42, Aβ40, WBV, VV, and HCV were analyzed separately using a series of analysis of covariance (ANCOVA) models. For each biomarker, the analysis was performed in patients who were in 1 of the 3 groups defined above and had a baseline measurement of the corresponding biomarker. The response variable was the biomarker at baseline. The distributions of CSF biomarkers were highly skewed. These biomarkers were log-transformed before the statistical analyses. The main factor of interest in the model was group. Age, sex, number of \(\text{APOE} \varepsilon4\) alleles, dose of bapineuzumab, and corresponding CSF biomarker (in log scale) at baseline were included in the models as covariates. The correlations among repeated measures were modeled with an unstructured covariance matrix. The differences in changes in biomarkers among the 3 groups were assessed by \(t\) tests contrasting the LS mean estimates of the 3 groups.

All analyses were performed using SAS 9.2 (sas.com).

**Standard protocol approvals, registrations, and patient consents**

Bapineuzumab noncarrier and carrier studies were registered on ClinicalTrials.gov (NCT00575055 and NCT00574132) and EudraCT (2009-012748-17). Prior to participation, each site’s institutional review board or ethics committee approved the study, and each participant (or legally authorized representative) gave written informed consent.

**Results**

In the bapineuzumab \(\text{APOE} \varepsilon4\) noncarrier and carrier studies, a total of 1,512 participants participated in one or more of the biomarker substudies. Of these, 909 were in the bapineuzumab group (154 with ARIA-E and 755 non-ARIA-E), while 593 were in the placebo group (non-ARIA-E) (figure 1). \(\text{APOE} \varepsilon4\) carrier frequency was higher in bapineuzumab ARIA-E participants compared with bapineuzumab non-ARIA-E participants (58% vs 46%; \(p = 0.0057\); table). Further, there was a higher proportion of \(\text{APOE} \varepsilon4\) homozygotes in performed in patients who were in one of the 3 groups defined above, had a baseline measure of the biomarker, and had a postbaseline measure of the biomarker collected after the onset of first ARIA-E. The response variable was the change in biomarker at all postbaseline visits. All models included the following fixed effects: visit, group, visit by group interaction, age, sex, number of \(\text{APOE} \varepsilon4\) alleles, and dose of bapineuzumab (0.5, 1, or 2 mg). The model for \(^{11}\text{C-PiB PET GCA SUVr}\) also included baseline GCA SUVr as a fixed effect. The models for BBSI, VBSI, and HBSI also included numbers of small (<10 mm) or large (≥10 mm) hemosiderin deposits at baseline and white matter hyperintensity score at baseline as fixed effects. The correlations among repeated measures were modeled with an unstructured covariance matrix. The differences in changes in biomarkers among the 3 groups were assessed by \(t\) tests contrasting the LS mean estimates of the 3 groups.
bapineuzumab ARIA-E participants (26.0% vs 8.6%), but no differences in age, sex, race, or baseline MMSE compared to bapineuzumab or placebo non-ARIA-E participants (table).

Comparing baseline brain PET amyloid signal (GCA SUVr) between ARIA-E and non-ARIA-E groups, no differences were observed for all participants with PiB PET data ($p > 0.56$; figure 2A), for those with baseline GCA SUVr >1.35 ($p > 0.29$; figure 2C), or between groups for individual study comparisons (figures e-2, A and C, and e-3, A and C, links.lww.com/WNL/A213). Bapineuzumab-treated participants who developed ARIA-E showed greater reduction at week 71 in PiB PET signal compared with non-ARIA-E participants ($p < 0.0016$; figure 2B). A similar pattern was observed for participants with baseline GCA SUVr >1.35 ($p < 0.0023$; figure 2D) and for $APOE e4$ carriers (figure e-2, B and D). For the $APOE e4$ noncarriers, a numerically greater reduction in PiB PET signal was observed in ARIA-E participants, but was not statistically significant (figure e-3, B and D).

No differences between ARIA-E and non-ARIA-E participants were observed in the baseline WBV, VV, or HCV ($p > 0.095$; figure 3, A, C, and E) with the exception of greater VV in ARIA-E vs placebo non-ARIA-E participants ($p = 0.049$; figure 3C). No differences were observed between groups for baseline WBV, VV, or HCV for individual study comparisons (figures e-4, A and C; e-5, A and C; and e-6, A and C, links.lww.com/WNL/A213). Greater ventricular

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**Table** Demographics and baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>Bapineuzumab ARIA-E (n = 154)</th>
<th>Bapineuzumab non-ARIA-E (n = 755)</th>
<th>Placebo non-ARIA-E (n = 595)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, y, mean (SD)</strong></td>
<td>71.2 (8.1)</td>
<td>72.1 (9.0)</td>
<td>71.3 (9.5)</td>
</tr>
<tr>
<td><strong>Sex, n (% female)</strong></td>
<td>66 (42.9)</td>
<td>359 (47.5)</td>
<td>267 (44.9)</td>
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<tr>
<td><strong>Race, n (% white)</strong></td>
<td>149 (96.8)</td>
<td>697 (92.3)</td>
<td>560 (94.1)</td>
</tr>
<tr>
<td><strong>$APOE e4$, n (%)</strong></td>
<td>90 (58.5)</td>
<td>349 (46.2)</td>
<td>286 (48.1)</td>
</tr>
<tr>
<td><strong>Heterozygote $e4$, n (%)</strong></td>
<td>50 (32.5)</td>
<td>284 (37.6)</td>
<td>214 (36.0)</td>
</tr>
<tr>
<td><strong>Homozygote $e4$, n (%)</strong></td>
<td>40 (26.0)</td>
<td>65 (8.6)</td>
<td>72 (12.1)</td>
</tr>
<tr>
<td><strong>Baseline MMSE total score, mean (SD)</strong></td>
<td>20.9 (3.0)</td>
<td>21.1 (3.2)</td>
<td>21.1 (3.1)</td>
</tr>
</tbody>
</table>

Abbreviations: ARIA-E = amyloid-related imaging abnormalities—edema or effusion; MMSE = Mini-Mental State Examination.
enlargement (VBSI) and hippocampal volume reduction (HBSI) were observed at week 71 in ARIA-E vs non-ARIA-E participants (all comparisons \( p < 0.001 \); figure 3, D and F). Similarly, greater VBSI and HBSI were observed at week 71 in ARIA-E vs non-ARIA-E participants for individual study comparisons (figure e-5, B and D; e-6, B and D). No differences were observed in whole brain volume reduction (BBSI) at week 71 between ARIA-E and non-ARIA-E groups (\( p > 0.58 \); figure 3B) or between groups for individual study comparisons (figure e-4, B and D).

Greater reductions at week 71 in CSF p-tau and t-tau (all comparisons \( p < 0.001 \); figure 4, F and H) were seen for No differences in baseline CSF A\( \beta \)\(_{42} \), or A\( \beta \)\(_{40} \), p-tau, or t-tau between groups were observed (all comparisons \( p > 0.089 \); figure 4, A, C, E, and G) or for individual study comparisons (figures e-7C; e-8, A and C; e-9, A and C; and e-10, A and C, links.lww.com/WNL/A213), except for lower CSF A\( \beta \)\(_{42} \) in APOE e4 noncarrier ARIA-E vs non-ARIA-E participants (figure e-7A).
Comparison of brain volumes between bapineuzumab (Bapi) ARIA-E vs Bapi or placebo (Pbo) non-ARIA-E groups for (A) baseline whole brain volumes (WBV), (B) change from baseline to week 71 WBV by boundary shift integral (BBSI), (C) baseline ventricular volumes (VV), (D) change from baseline to week 71 VV by ventricular boundary shift integral (VBSI), (E) baseline hippocampal volumes (HV), and (F) change from baseline to week 71 HV by hippocampal boundary shift integral (HBSI). Data plotted are least square (LS) means ± 1 standard error.
ARIA-E vs non-ARIA-E participants and were similarly observed between groups in individual study comparisons (figures e-9, B and D, and e-10, B and D, links.lww.com/WNL/A213). There was a greater reduction at week 71 in CSF Aβ40 concentrations for ARIA-E vs non-ARIA-E participants ($p < 0.05$; figure 4D) and in carrier (figure e-8, D) but not for noncarrier comparisons (figure e-8, B). No differences at week 71 were observed for CSF Aβ42 between ARIA-E and non-ARIA-E participants (figure 4B) or for individual study comparisons (figure e-7, B and D).
Discussion

ARIA are imaging-defined phenomena observed with anti-amyloid therapies for AD; ARIA-E refers to changes seen on FLAIR MRI that are thought to represent cerebral parenchymal edema and sulcal effusions. ARIA-E may rarely occur spontaneously but is much more frequent with therapies directed against cerebral amyloid, especially with anti-amyloid immunotherapy using antibodies directed against aggregated/fibrillar Aβ. ARIA are usually asymptomatic and typically resolve within 3 months but importantly can be dose-limiting for therapeutic trials. The present study evaluated whether the occurrence of ARIA-E is associated with specific biomarker patterns at baseline or longitudinally in 2 phase 3 trials with bapineuzumab. The incidence of ARIA-E (~10%) in the biomarker substudy participants was similar to that in the parent trials.

Generally, baseline biomarker status (brain amyloid burden on PiB PET; brain, ventricular, and hippocampal volumes on MRI; CSF p-tau, t-tau, Aβ40, and Aβ42) was not associated with development of ARIA-E. However, APOE ε4 noncarrier participants who developed ARIA-E had lower baseline CSF Aβ42 concentrations (and nonsignificant greater ventricular volumes). Reduced CSF Aβ42 is a marker of AD pathology and correlates, inversely, with cortical amyloid deposition evaluated by amyloid PET. This APOE gene–dose-dependent association is seen in elderly, but not in younger, individuals, irrespective of clinical status, but is not present when stratified for amyloid PET status, further supporting that low CSF Aβ42 may be a more sensitive indicator of brain amyloid positivity than amyloid PET. Indeed, baseline amyloid PET was not found to be increased in the noncarriers with ARIA-E. The lack of difference in baseline amyloid PET between groups may also be due to the low numbers who underwent PiB PET and that few had both PET and CSF assessments, resulting in nonoverlapping analysis populations.

A greater baseline ventricular volume was observed for ARIA-E participants compared with the placebo non-ARIA-E participants, a difference largely driven by the noncarrier participants. The fact that bapineuzumab-treated participants who developed ARIA-E did not have larger ventricles than bapineuzumab-treated participants who did not develop ARIA-E suggests that ventricular enlargement is not a specific risk factor for ARIA-E.

In terms of longitudinal changes, bapineuzumab-treated participants who developed ARIA-E had a reduction in amyloid burden (PiB PET) compared to those who did not develop ARIA-E.

Previous reports have suggested a relationship between brain areas with ARIA-E and localized amyloid clearance. Although this study did not evaluate regional, localized associations between ARIA-E and PiB PET changes, the reductions in global SUVr over the 18-month study were clearly significant in the bapineuzumab-treated ARIA-E group despite relatively small numbers in each group. In contrast, there was a lack of change from baseline in the non-ARIA-E groups.

The ARIA-E participants also had a greater reduction in total hippocampal volume (indexed by greater HBSI) and a significantly greater ventricular volume increase (indexed by a greater VBSI) compared to both the bapineuzumab non-ARIA-E and placebo non-ARIA-E groups. These changes appeared early in the study: by week 19, the majority of the volumetric differences between the ARIA-E and the non-ARIA-E groups were already present. Differences were similar in magnitude for brain volume changes (BBSI), though they did not reach statistical significance. One explanation for these volumetric changes is that they are due to a greater removal of amyloid plaques and the reduction in plaque-associated pathology (e.g., inflammatory changes) in ARIA-E participants, as suggested by the greater reduction in PiB PET signal. This might be expected to reduce brain parenchymal volume and cause an ex vacuo expansion of the ventricles. Thus, the increased ventricular enlargement in ARIA-E participants (VBSI difference of 2.9 mL [95% confidence interval (CI) 1.7–4.2] compared with bapineuzumab non-ARIA-E participants and 3.8 mL [95% CI 2.6–5.1] compared with placebo non-ARIA-E) could have resulted from a change of as little as ~0.3–0.4% of total brain volume.

Another potential cause of volumetric change that must be considered is an accelerated rate of neurodegeneration in participants who experienced ARIA-E; several findings counter this explanation, including a lack of difference in clinical outcomes between ARIA-E and non-ARIA-E groups and the greater reduction in CSF p-tau and t-tau in ARIA-E participants. Although there were more APOE ε4 homozygotes among ARIA-E participants, volumetric differences were similar when APOE ε4 carriers and noncarriers were examined separately.

Finally, it has been suggested that mobilization of β-amyloid from plaques may result in its transient deposition in perivascular spaces; this in turn blocks perivascular flow of interstitial fluid, leading to interstitial edema (ARIA-E) with eventual resolution through drainage of the excess fluid into the lateral ventricles. While this may explain a proportion of ventricular volume increase, it would not be pertinent for the greater reduction in hippocampal volume.

The greater reductions in CSF p-tau and t-tau in ARIA-E compared with non-ARIA-E groups may indicate that ARIA-E, except for being an MRI finding, is a marker for better treatment response (as also supported by the PET findings), with reductions towards normalization of the downstream biomarkers p-tau and t-tau.

The main limitation for this study was the small sample size for most comparisons. There were only 154 ARIA-E cases in

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In this study, baseline biomarkers do not predict risk for developing ARIA-E, except perhaps in APOE ε4 noncarriers showing greater evidence of Aβ accumulation (lower CSF Aβ42). ARIA-E was associated with several significant longitudinal biomarker changes including reduction in amyloid deposition and lower CSF markers of downstream neurodegeneration. Somewhat paradoxically, ARIA-E also appeared to be associated with early increases in ventricular volume and reductions in hippocampal volume. These findings suggest that efflux of Aβ from the brain parenchyma associated with ARIA-E might influence downstream disease pathogenic processes and may shed light on the mechanism of action of bapineuzumab.

**Author contributions**

E. Liu, G. Novak, J. Streffer, S. Einstein, M. Schmidt, H.R. Brashear: study concept and design, study supervision and coordination, acquisition of data, analysis and interpretation of data, drafting/revising manuscript for content. R. Sperling, S. Salloway: study concept and design, analysis and interpretation of data, drafting/revising manuscript for content. P. Scheltens, N.C. Fox, K. Blennow: analysis and interpretation of data, drafting/revising manuscript for content. D. Wang: analysis and interpretation of data, statistical analysis, drafting/revising manuscript for content. K. Booth: study concept and design, manuscript review and content revision. N. Ketter: MRI ARIA-E data review and interpretation, manuscript review, content revision.

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**Study funding**

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**Disclosure**

E. Liu was an employee of Janssen Research and Development, LLC, at the time the studies were conducted and the manuscript initiated and is now an employee of Prothena Biosciences, Inc. D. Wang is an employee of Janssen Research and Development, LLC. R. Sperling has served as a consultant for Roche, Janssen, Lundbeck, Genentech, Bracket, Sanofi, AbbVie, and Biogen. She has received research support from Eli Lilly and Company and Janssen Research and Development. S. Salloway is a consultant to Janssen Alzheimer Immunotherapy, Avid/Lilly, GE Healthcare, AstraZeneca, Biogen, Roche, iPiieran, Novartis Pharmaceuticals Corporation, Merck, and Piramal. His hospital receives research support for the conduct of clinical trials sponsored by Janssen Alzheimer Immunotherapy, Lilly, Merck, Roche, Functional Neuromodulation, Biogen, Genentech, Avid, and GE Healthcare. N. Fox has provided consultancy to Janssen Alzheimer Immunotherapy and UCL received payment for MRI analysis. His research group has also received payment for consultancy or for conducting studies from AVID, Bristol-Myers Squibb, Elan, Eisai, Lilly, GE Healthcare, IXICO, Johnson & Johnson, Lundbeck, Novartis Pharmaceuticals Corporation, Pfizer, Sanofi, and Wyeth. Dr. Fox receives no personal compensation for the aforementioned activities. K. Blennow receives research support to his laboratory from Janssen Alzheimer Immunotherapy for collaborative projects, and has served at advisory boards and for consultancy for IBL International, Fujirebio Europe, Novartis, Roche Diagnostics, Eli Lilly, Agen, Sanofi-Aventis, and Alzheon. P. Scheltens’ research group received research support from Merck, GE, and Piramal. His research group has also received payment for consultancy or for conducting studies from Roche, Novartis, Forum, Lilly, Sanofi, and Probiodrug. Dr. Scheltens receives no personal compensation for these activities. M. Schmidt is an employee of Janssen Research and Development, LLC. J. Streffer is an employee of Janssen Research and Development, LLC. G. Novak is an employee of Janssen Research and Development, LLC. S. Einstein is an employee of Janssen Research and Development, LLC. K. Booth is an employee of Pfizer, Inc. N. Ketter was an employee of Janssen Research and Development, LLC, at the time the studies were conducted and the manuscript initiated and is now retired. H. Brashear is an employee of Janssen Research and Development, LLC. Go to Neurology.org/N for full disclosures.

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**References**


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Study question
Is the observed occurrence of amyloid-related imaging abnormalities with edema/effusion (ARIA-E) in clinical trials of bapineuzumab associated with specific biomarker patterns?

Summary answer
Longitudinal changes in various biomarkers were associated with incident ARIA-E.

What is known and what this paper adds
Incident ARIA-E has been reported in clinical trials of bapineuzumab and is associated with the presence of APOE ε4 alleles. This study elucidates the biomarkers associated with the development of ARIA-E in patients receiving bapineuzumab.

Participants and setting
This study analyzed 1,504 patients with probable Alzheimer disease who participated in phase 3 clinical trials of bapineuzumab. They either did (n = 725) or did not (n = 779) carry APOE ε4 alleles.

Design, size, and duration
Phase 3 clinical trial data were retrospectively analyzed for patients who received bapineuzumab (n = 909) or a placebo (n = 595). These data included subsets with 11C-PiB PET scans, which reflected β-amyloid (Aβ) levels; MRI scans, which reflected global and regional brain volumes; and CSF measurements of specific forms of tau and Aβ. The study assessed longitudinal changes in these measurements as predictive biomarkers for the primary outcome.

Primary outcomes
The primary outcome was developing ARIA-E during the study.

Main results and the role of chance
There were 154 cases of incident ARIA-E in the bapineuzumab-treated group. Compared to bapineuzumab-treated participants without ARIA-E, those with ARIA-E were more likely to carry APOE ε4 alleles (46% vs 58%; p = 0.0057). In week 71, compared to placebo- and bapineuzumab-treated participants without ARIA-E, participants with ARIA-E had greater reduction in brain amyloid burden by 11C-PiB PET (p = 0.0016), greater ventricular enlargement and hippocampal volume reduction (p < 0.001 for both), and greater reductions in CSF levels of phosphorylated tau (p < 0.001), total tau (p < 0.001), and Aβ40 (p < 0.05).

Bias, confounding, and other reasons for caution
The study included only 154 participants with ARIA-E. The study did not account for when the participants developed ARIA-E. Lack of complete biomarker data for all participants limited the analyses.

Generalizability to other populations
Data from placebo-treated participants with ARIA-E were excluded. This may limit generalizability to patients who spontaneously develop ARIA-E.

Study funding/potential competing interests
This study was funded by Janssen Pharmaceuticals and Pfizer. The authors report receiving employment, consultancy work, and research support from various pharmaceutical companies. Go to Neurology.org/N for full disclosures.

A draft of the short-form article was written by M. Dalefield, a writer with Editage, a division of Cactus Communications. The authors of the full-length article and the journal editors edited and approved the final version.
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