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Amyloid-β ^{11}C-PiB-PET imaging results from 2 randomized bapineuzumab phase 3 AD trials

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ABSTRACT

Objective: To evaluate the effects of bapineuzumab on brain β-amyloid (Aβ) burden using ^{11}C-Pittsburgh compound B (^{11}C-PiB)-PET.

Methods: Two phase 3 clinical trials, 1 each in apolipoprotein *APOE* ε4 carriers and noncarriers, were conducted in patients with mild to moderate Alzheimer disease dementia. Bapineuzumab, an anti-Aβ monoclonal antibody, or placebo, was administered by IV infusion every 13 weeks for 78 weeks. PET substudies assessed change in brain fibrillar Aβ over 71 weeks using an ^{11}C-PiB-PET standardized uptake value ratio (SUVr) global cortical average (GCA) comprising the average SUVr from 5 cortical regions of interest with cerebellar gray matter as the reference region.

Results: A total of 115 carriers and 39 noncarriers were analyzed. The difference (δ) in mean baseline to 71 week change in ^{11}C-PiB-PET GCA between bapineuzumab and placebo was significant in carriers (0.5 mg/kg vs placebo δ = −0.101; p = 0.004) and in pooled analyses of both carriers and noncarriers (0.5 mg/kg vs placebo δ = −0.068; p = 0.027; 1.0 mg/kg vs placebo δ = −0.133; p = 0.028) but not in the noncarrier trial separately. Analyses by individual region of interest and in mild disease yielded findings similar to the main trial results.

Conclusions: The ^{11}C-PiB-PET imaging results demonstrated reduction of fibrillar Aβ accumulation in patients with Alzheimer disease treated with bapineuzumab; however, as no clinical benefit was observed, the findings are consistent with the hypotheses that bapineuzumab may not have been initiated early enough in the disease course, the doses were insufficient, or the most critical Aβ species were inadequately targeted. *Neurology*® 2015;85:692–700

GLOSSARY

Aβ = β-amyloid; **AD** = Alzheimer disease; **ARIA** = amyloid-related imaging abnormalities; **GCA** = global cortical average; **MMSE** = Mini-Mental State Examination; **NINCDS-ADRDA** = National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association; **PiB** = Pittsburgh compound B; **ROI** = region of interest; **SUVr** = standardized uptake value ratio.

Bapineuzumab, a humanized monoclonal antibody targeting the N-terminus of β-amyloid (Aβ), was recently evaluated in phase 3 trials for the treatment of mild to moderate Alzheimer disease (AD) dementia. As part of those investigations, brain volumetric MRI, brain amyloid PET imaging, and CSF sampling were performed in biomarker substudies. The primary aim of the substudies was to assess the pharmacologic effects of bapineuzumab on AD CNS biomarkers. The PET substudy used ^{11}C-Pittsburgh compound B (^{11}C-PiB)-PET as a measure of brain fibrillar Aβ.[1] Differences in the incidence of amyloid-related imaging abnormalities (ARIA) and potential efficacy signals had been seen between participants treated with bapineuzumab who were *APOE* ε4 carriers and noncarriers in phase 2 studies[2–4]; therefore, separate clinical trials for *APOE* ε4 carriers (Study 302) and noncarriers (Study 301) were conducted in phase 3. The primary clinical and biomarker endpoint results of these trials were recently

reported.[5] We report additional analyses of the ^{11}C-PiB-PET data that evaluate the effects of *APOE* ε4 status and disease severity, pooled analyses of the carrier and noncarrier studies, individual regions of interest (ROI), and a sensitivity analysis using the pons as a reference region instead of cerebellar gray matter.

METHODS **Patients.** Enrollment criteria and randomization scheme for the bapineuzumab PiB-PET substudies were the same as for the main studies described previously.[5] In brief, eligible patients were aged 50–88 years inclusive, met National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) clinical criteria for probable AD,[6] had a Mini-Mental State Examination (MMSE)[7] score of 16–26, and had a modified Hachinski Ischemic Score ≤4.[8] Patients were excluded for clinically significant neurologic disease other than AD.

Standard protocol approvals, registrations, and patient consents. The institutional review board for each site approved the study, and each participant (or legally authorized representative) gave written informed consent before enrollment.

In the *APOE* ε4 carrier study, 1,121 participants were randomized in a ratio of 3:2 bapineuzumab 0.5 mg/kg placebo. In the noncarrier study, 1,331 participants were randomized in a ratio of 1:1:1:2 bapineuzumab 0.5 mg/kg 1.0 mg/kg 2.0 mg/kg placebo. However, the 2.0 mg/kg dose was discontinued early in the trial owing to safety events (symptomatic ARIA); participants randomized to that dose were excluded from the PET substudy analysis (figure e-1 on the *Neurology*® Web site at Neurology.org). Randomization stratification factors were current cholinesterase inhibitor or memantine use; baseline MMSE total score (low = 16–21 vs high = 22–26); and, in the carrier study, *APOE* ε4 copy number (1 vs 2). Patients received study drug 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 administered intravenously compared with placebo by measuring the change from baseline to week 78 in clinical endpoints. An important secondary objective was to evaluate the effect of bapineuzumab on change in standardized uptake value ratio (SUVr) from baseline to week 71 in brain Aβ burden using ^{11}C-PiB-PET in a substudy of approximately 10% of enrolled participants. Exploratory objectives were to evaluate the effect of bapineuzumab on ^{11}C-PiB-PET change in participants with mild and moderate disease separately (defined by baseline MMSE ranges of 22–26 and 16–21, respectively) in pooled analyses using all analyzable patients from both the carrier and noncarrier studies and in individual brain ROIs. Finally, the effect of using the pons as an alternative reference region to the cerebellar gray matter was evaluated in a prespecified analysis.

[11]C-PiB-PET scans were obtained at baseline, week 45, and week 71. Imaging was conducted at 14 US academic PET centers, almost all having prior experience with ^{11}C-PiB-PET imaging in AD. All sites underwent a study-specific site qualification process. Several different PET or PET/CT cameras were used although centers were requested to scan participants with the same camera throughout the study. Cameras had to be capable of emission data collection in 3 dimensions and have an axial field of view sufficient for imaging the entire brain in a single bed position. Centers had to provide Hoffman phantom data of suitable quality. Camera-specific acquisition, emission correction, and reconstruction settings were adopted from the Alzheimer's

Disease Neuroimaging Initiative (http://www.adni-info.org/Scientists/ADNIStudyProcedures.aspx). Best local practices were used to ensure that participants remained in the field of view with minimal movement during scanning.

[11]C-PiB was prepared in accordance with documented manufacturing and control information, and quality was reviewed during the course of the trial. A target ^{11}C-PiB dose of 555 MBq (15 mCi) (accepted range: 370–610 MBq [10–16.5 mCi]) was injected over ≤30 seconds. Emission data were collected as four 5-minute frames from 50 to 70 minutes post-tracer injection[1]; attenuation data were acquired using procedures appropriate to PET-only or PET/CT cameras and were used for image reconstruction by the site. Baseline 3D T1 MRI scans for each participant were obtained for use in PiB-PET analyses.

Reconstructed PET scans and baseline 3D T1 MRI scans for each participant were transferred from acquisition sites for quality review and only images determined to be of suitable quality for quantitative analysis were included.

Image analysis. The second through fourth frames comprising the reconstructed ^{11}C-PiB-PET scans for each participant were rigidly registered to the first frame to account for movement between frames and then averaged.

The BrainWeb 3D T1 MRI (http://brainweb.bic.mni.mcgill.ca/brainweb/)[9] was nonrigidly registered to the participant's 3D T1 MRI,[10,11] and this transformation was used to map the following ROIs to the participant's 3D T1 MRI: the Automated Anatomical Labelling atlas,[12] an ROI defined for cerebellar gray matter with the inferior 10 mm truncated to exclude less reliable emission data from the edge of the field of view, and the pons. The participant's 3D T1 MRI was then segmented into gray and white matter tissue masks.[13] Finally, the participant's 3D T1 MRI was rigidly registered to the PET, and this transformation was used to map all ROIs and tissue masks onto the participant's registered and averaged PET. Final ROIs were defined as the intersection of the ROIs and tissue masks in PET space.

Five cerebral regions known to accumulate substantial fibrillar Aβ in AD (anterior cingulate, posterior cingulate/precuneus, frontal, lateral temporal, and parietal cortex) were considered primary for evaluating treatment effects. Individual regional SUVrs were calculated as the ratio of tissue activity for each ROI to the tissue activity of the reference region: cerebellar gray matter for the prespecified analysis in the statistical analysis plan and pons as an additional prespecified analysis in the study imaging charter. The global cortical average (GCA) SUVr was constructed from the unweighted average of the SUVrs from these 5 individual cerebral ROIs. Additional ROIs (mesial temporal cortex, occipital, striatum, and thalamus) were included in separate individual ROI analysis.

Sample size. In the carrier study, acquisition of PiB-PET data for 32 participants in the placebo group and 48 participants in the bapineuzumab group was estimated to provide 90% power to detect a 0.152 SUVr unit reduction in Aβ burden for the bapineuzumab group compared with placebo at week 71. In the noncarrier study, 45 participants in the placebo group and 25 participants in each of the 2 bapineuzumab groups were estimated to provide >90% power to detect a 0.186 SUVr unit reduction in amyloid burden for a bapineuzumab group compared with placebo at week 71. The sample size calculations were based on 2-sided tests with α set at 0.05. The standard deviations for both studies (0.203) were estimated from a previous bapineuzumab study.[3]

Analysis specifications. ^{11}C-PiB-PET GCA analyses were performed on a modified intent-to-treat population and included

Figure 1   Distribution of ¹¹C–Pittsburgh compound B-PET global cortical average at baseline among *APOE* ε4 carriers and noncarriers
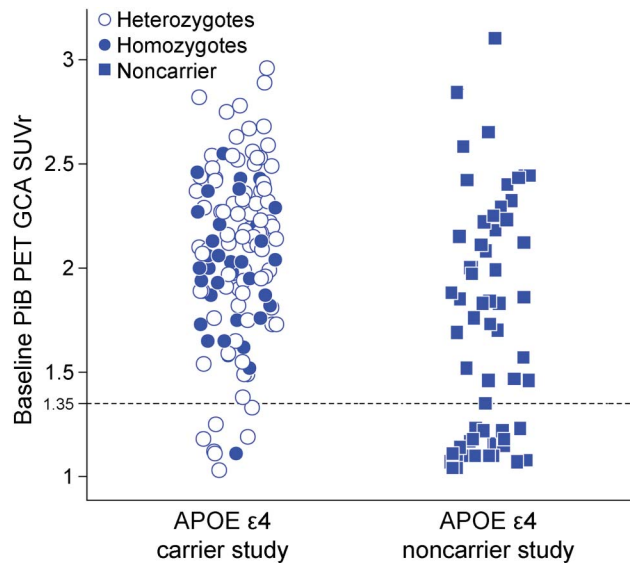
A total of 6.5% (8/123) of *APOE* ε4 carriers had baseline scans with global cortical average (GCA) <1.35 compared with 36.1% (21/61) of noncarriers. PiB = Pittsburgh compound B; SUVr = standardized uptake value ratio.

only participants who received at least part of 1 infusion and had a baseline, and at least 1 postbaseline, ¹¹C-PiB-PET assessment.

Change-from-baseline analyses were further restricted to participants who also had a baseline GCA ≥1.35 (referred to as the PiB-PET analysis population) to allow for a potential reduction in ¹¹C-PiB to be observed. ¹¹C-PiB GCA values <1.35 were considered amyloid-negative.

Unless otherwise noted, change from baseline was analyzed using a restricted maximum likelihood–based mixed model for repeated measures. The response variable was the change from baseline to each postbaseline visit, and the primary endpoint was the change from baseline to week 71. The model included the following fixed effects: treatment (with 2 levels, bapineuzumab and placebo, in carriers; with 3 levels, bapineuzumab 0.5 mg/kg, bapineuzumab 1.0 mg/kg, and placebo, in noncarriers and pooled analyses), visit (scheduled, a categorical factor), treatment-by-visit interaction, baseline GCA (a numerical covariate), baseline-by-visit interaction, baseline MMSE total score stratum (with 2 levels, low ≤21 and high ≥22), baseline cholinesterase inhibitor or memantine use stratum (with 2 levels, yes and no), and baseline age (a numerical covariate). *APOE* ε4 copy number stratum was included in the carrier study (with 2 levels, 1 copy and 2 copies) whereas *APOE* ε4 carrier status (carrier or noncarrier) was included in the pooled study analyses. An unstructured variance-covariance structure was used to model the within-subject errors. Estimates are reported as mean ± SE unless otherwise noted. Reported *p* values are unadjusted for multiple comparisons; *p* values <0.05 were considered nominally significant.

RESULTS Participant disposition is summarized in figure e-1. In the carrier study, 155 of 1,121 randomized participants were enrolled in the placebo (n = 60) and 0.5 mg/kg (n = 95) treatment groups of the PET substudy. In the noncarrier study, 84 of 1,331 randomized participants were enrolled in the placebo (n = 33), 0.5-mg/kg (n = 26), and 1.0-mg/kg

(n = 25) treatment groups of the PET substudy. The mean (SD) baseline GCA was 2.07 (0.403) for carriers and 1.72 (0.548) for noncarriers (*p* < 0.001, *t* test). The baseline GCA distributions for carriers and noncarriers with postbaseline PET measures are illustrated in figure 1. Data for 6.5% of carriers and 36.1% of noncarriers were excluded from the change-from-baseline analyses owing to a baseline GCA less than the prespecified threshold for inclusion (1.35), resulting in 115 carrier participants (40 receiving placebo and 75 receiving 0.5 mg/kg) and 39 noncarrier participants (15 receiving placebo, 12 receiving 0.5 mg/kg, 12 receiving 1.0 mg/kg) in the PiB-PET analysis population. The mean (SD) baseline GCAs were similar for carriers (2.14 ± 0.333) and noncarriers (2.05 ± 0.400) in the PiB-PET analysis population (*p* = 0.18). The baseline demographics, clinical characteristics, and GCAs of the PiB-PET analysis population were similar between the treatment and placebo groups (table 1).

The key PET results for each study, for both studies combined, and for the mild and moderate AD subgroups, derived using the PiB-PET analysis population, are shown in figure 2 (figures e-2 and e-3 show individual participant data). Among carriers (figure 2A), a baseline to 71 week increase in GCA was observed in the placebo group (mean ± SE 0.102 ± 0.026) but not in the bapineuzumab group (mean ± SE 0.001 ± 0.021), resulting in a significant treatment difference (δ) in the baseline to week 71 change in mean GCA between groups (δ = −0.101; *p* = 0.004). The baseline to week 71 increase (sample mean ± SE) in GCA among placebo carriers was similar among heterozygote (0.13 ± 0.034) and homozygote *APOE* ε4 carriers (0.08 ± 0.038). In noncarriers, a modest baseline to week 71 decrease in mean GCA was observed in the placebo group (−0.046 ± 0.0443), with no statistically significant treatment differences for either the 0.5-mg/kg (δ = 0.085, *p* = 0.193) or the 1.0-mg/kg groups (δ = −0.048, *p* = 0.466) compared with placebo (figure 2B). In the pooled study analysis that included participants from both studies (figure 2C), the baseline to week 71 ¹¹C-PiB-PET changes for placebo, 0.5 mg/kg, and 1.0 mg/kg, respectively, were 0.072 ± 0.023, 0.004 ± 0.019, and −0.061 ± 0.055, with treatment differences compared with placebo observed for both the 0.5-mg/kg (δ = −0.068; *p* = 0.027) and 1.0-mg/kg (δ = −0.133; *p* = 0.028) doses. The treatment differences observed in the carrier study and in the pooled analysis were most pronounced in the mild subgroup (figure 2, D and F). No significant differences were observed in the moderate subgroup, either in the individual study or pooled study analyses.

The treatment-related difference in mean GCA observed from baseline to week 71 among carriers

Table 1 ^{11}C-PiB-PET analysis population (≥1.35 SUVr): Demographic and baseline characteristics

	Carriers		Noncarriers			Pooled carriers and noncarriers		
	Placebo (n = 40)	Bapineuzumab, 0.5 mg/kg (n = 75)	Placebo (n = 15)	Bapineuzumab, 0.5 mg/kg (n = 12)	Bapineuzumab, 1.0 mg/kg (n = 12)	Placebo (n = 55)	Bapineuzumab, 0.5 mg/kg (n = 87)	Bapineuzumab, 1.0 mg/kg (n = 12)
Age, y, mean (SD)	70.1 (8.4)	71.1 (8.0)	71.5 (11.3)	67.1 (11.2)	75.8 (11.23)	70.5 (9.15)	70.6 (8.51)	75.8 (11.23)
No. (%) female	29 (72.5)	39 (52.0)	5 (33.3)	4 (33.3)	5 (41.7)	34 (61.8)	43 (49.4)	5 (41.7)
Race, n (%) Caucasian	38 (95.0)	70 (93.3)	15 (100)	12 (100)	11 (91.7)	53 (96.4)	82 (94.3)	11 (91.7)
AChEI or memantine use, n (%)	39 (97.5)	72 (96.0)	13 (86.7)	11 (91.7)	11 (91.7)	50 (90.9)	83 (95.4)	11 (91.7)
MMSE total score, mean (SD)	20.3 (3.2)	21.3 (3.3)	19.8 (3.2)	21.0 (2.9)	22.2 (3.1)	20.2 (3.1)	21.3 (3.2)	22.2 (3.1)
ADAS-Cog 11 total score, mean (SD)	22.5 (9.4)	22.0 (9.1)	22.5 (8.6)	21.3 (5.0)	19.8 (7.6)	22.5 (9.1)	21.9 (8.6)	19.8 (7.6)
DAD total score, mean (SD)	84.5 (15.8)	82.2 (17.4)	80.4 (20.2)	87.2 (11.4)	78.4 (18.9)	83.4 (7.0)	82.9 (16.8)	78.4 (18.9)
GCA SUVr, mean (SD)	2.11 (0.34)	2.16 (0.33)	2.09 (0.40)	2.16 (0.40)	1.90 (0.39)	2.10 (0.35)	2.16 (0.34)	1.90 (0.39)

Abbreviations: AChEI = acetylcholinesterase inhibitor; ADAS-Cog = Alzheimer's Disease Assessment Scale–Cognitive component; DAD = Disability Assessment for Dementia; GCA SUVr = global cortical average standardized uptake value ratio; MMSE = Mini-Mental State Examination; PiB = Pittsburgh compound B; SUVr = standardized uptake value ratio.

was consistent with the 5 individual ROI analyses (table 2). Treatment-related differences in the change from baseline to week 71 regional SUVrs were observed in the anterior cingulate, posterior cingulate/precuneus, and lateral temporal cortices, with trends observed in the frontal and parietal cortices. Treatment-related differences in the change from baseline to week 71 SUVrs were also observed in the mesial temporal and occipital cortices and subcortical regions of the thalamus and striatum. The lack of treatment-related differences in GCA change over 71 weeks observed in the noncarrier study was also seen in the individual region analysis, except for the subcortical regions at the 1.0 mg/kg dose, in which treatment-related differences in the change from baseline to week 71 SUVrs were observed (table 2).

Pooling data from the carrier and noncarrier studies, there was no evidence of ^{11}C-PiB-PET accumulation among Aβ-negative participants (baseline GCA < 1.35) at week 71, among either the placebo or treated groups (sample mean GCA change from baseline = 0.00 ± 0.011 for placebo, 0.01 ± 0.011 for treated participants).

A sensitivity analysis of the change in the mean GCA was also performed for each study using the pons as a reference region (figure 3). For carriers, there was a small increase in mean GCA for the placebo group (0.021 ± 0.0130), and a small decrease for the 0.5 mg/kg group (−0.023 ± 0.0102), resulting in a significant treatment-related difference in the baseline to week 71 change in GCA (δ = −0.044, p = 0.011). For noncarriers, there were no significant treatment-related differences in the baseline to week

71 change in ^{11}C-PiB-PET GCA for the 0.5-mg/kg (δ = −0.041, p = 0.387) or 1.0-mg/kg groups (δ = −0.085, p = 0.083); however, in this analysis there was no change in mean GCA SUVr for the placebo group at week 71 (0.00 ± 0.0320), in contrast to the modest decrease observed using the cerebellar reference region. Additionally, a modest decrease was observed in the baseline to week 71 change in GCA in the 0.5 mg/kg group.

DISCUSSION The totality of the data from the 2 phase 3 PET bapineuzumab substudies suggests that IV treatment with bapineuzumab reduced fibrillar Aβ accumulation relative to placebo over 71 week in mild to moderate AD dementia. This reduction was most clearly evident in the carrier study and the pooled analyses (which included both carriers and noncarriers) for both the 0.5- and 1.0-mg/kg doses. The observation that the treatment differences seen in the carrier and pooled analyses seem to have been driven primarily by participants with mild disease raises the possibility that bapineuzumab immunotherapy could have a greater effect on amyloid accumulation in patients treated earlier in the disease course. These results, together with CSF analyses[4] performed in patients treated with bapineuzumab, support the hypothesis that bapineuzumab can enter the brain and achieve exposures sufficient to engage its target, thereby altering fibrillar Aβ accumulation.

The prevalence of significant Aβ burden at baseline and subsequent change in GCA over the course of the study was lower for *APOE* ε4 noncarriers than carriers. The smaller than expected analyzable sample

Figure 2 Model-estimated effect of bapineuzumab on Aβ burden in carriers, noncarriers, pooled studies, and by disease severity
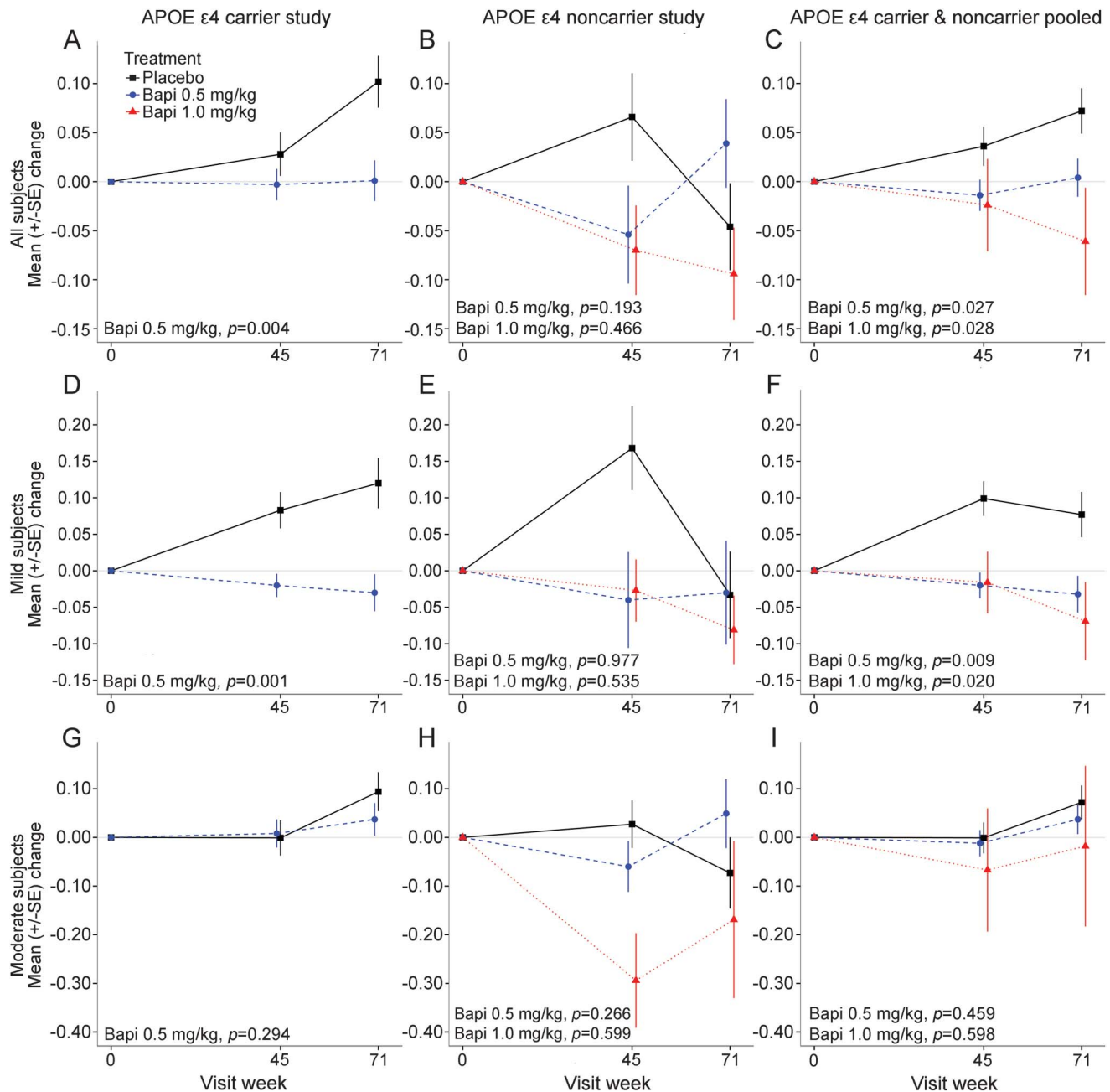
Treatment differences were observed in the carrier study and in the pooled study results. Treatment differences appeared more prominent in participants with mild disease (carrier placebo/bapineuzumab [Bapi]: A, 40/75; D, 18/40; G, 22/35; noncarrier placebo/0.5 mg/kg/1.0 mg/kg: B, 15/12/12; E, 7/6/9; H, 8/6/3; pooled placebo/0.5 mg/kg/1.0 mg/kg: C, 55/87/12; F, 25/46/9; I, 30/41/3).

and lack of ^{11}C-PiB accumulation over 71 weeks among noncarriers reduced the power of detecting treatment differences in amyloid burden reduction in the noncarrier study. The frequency of amyloid-negative scans in noncarriers (36%) in our study is similar to rates observed in phase 2 trials of florbeta-ben[14] and florbetapir[15] and phase 3 studies of solane-zumab.[16] The GCA in amyloid-negative participants did not change significantly over the course of the study. Although all participants met NINCDS-ADRDA criteria for probable AD, the absence of

significant Aβ burden in some participants entering the trial suggests that other disease processes might account for their cognitive impairment. Among placebo participants with baseline GCA ≥1.35, carriers showed an increase in ^{11}C-PiB signal over the course of the study, whereas noncarriers did not. Grimmer et al.[17] also found differences by *APOE* ε4 genotype in the progression of the cortical ^{11}C-PiB-PET signal in participants with AD over a 2-year interval. This finding may suggest that *APOE* ε4 has a sustained influence on Aβ

Region	Carriers		Noncarriers, 0.5 mg/kg vs placebo		Noncarriers, 1.0 mg/kg vs placebo	
	Treatment difference	p Value	Treatment difference	p Value	Treatment difference	p Value
GCA	−0.101	0.004[a]	0.085	0.193	−0.048	0.466
Anterior cingulate	−0.162	<0.001[a]	0.129	0.138	−0.101	0.256
Posterior cingulate/precuneus	−0.090	0.021[a]	0.110	0.171	−0.048	0.560
Frontal cortex	−0.096	0.099	0.057	0.455	−0.088	0.265
Lateral temporal cortex	−0.095	<0.001[a]	0.086	0.111	−0.051	0.343
Parietal cortex	−0.066	0.061	0.018	0.802	−0.005	0.942
Mesial temporal cortex	−0.075	<0.001[a]	0.044	0.230	−0.038	0.315
Occipital cortex	−0.055	0.027[a]	0.080	0.124	−0.009	0.865
Thalamus	−0.118	<0.001[a]	−0.094	0.075	−0.165	0.004[a]
Striatum	−0.149	<0.001[a]	0.012	0.819	−0.140	0.018[a]

Abbreviations: GCA = global cortical average; SUVr = standardized uptake value ratio.
The treatment difference refers to the estimated difference in the mean baseline to week 71 changes in ^{11}C–Pittsburgh compound B-PET global cortical average between the treatment groups.
[a] Significant.

accumulation and not just on the timing of its initiation and could also have implications regarding the use of amyloid PET in detecting treatment effects targeting Aβ deposition.

Treatment of *APOE* ε4 carriers was associated with significant differences in the change from baseline GCA over 71 weeks compared with placebo whether cerebellar gray or pons was used as the reference. In carriers, treatment-related decreases in Aβ burden were also observed in most brain regions when analyzed individually. Treatment of noncarriers with bapineuzumab did not show a significant

treatment difference in GCA change to week 71 regardless of whether the cerebellar gray or pons was used as the reference region. The variable pattern of GCA change over time observed with the use of different reference regions (figures 2, A and B, and 3) may indicate that the PiB-PET signal changed in one or both reference regions during the trial. Increased Aβ deposition in placebo or decreased deposition in treated participants within a reference region would lead to an underestimation of the treatment effect. The cause of the pattern of change in the placebo noncarriers (figure 2B) is not completely clear, but

Figure 3   Pons-based standardized uptake value ratio: model-estimated change from baseline to week 71
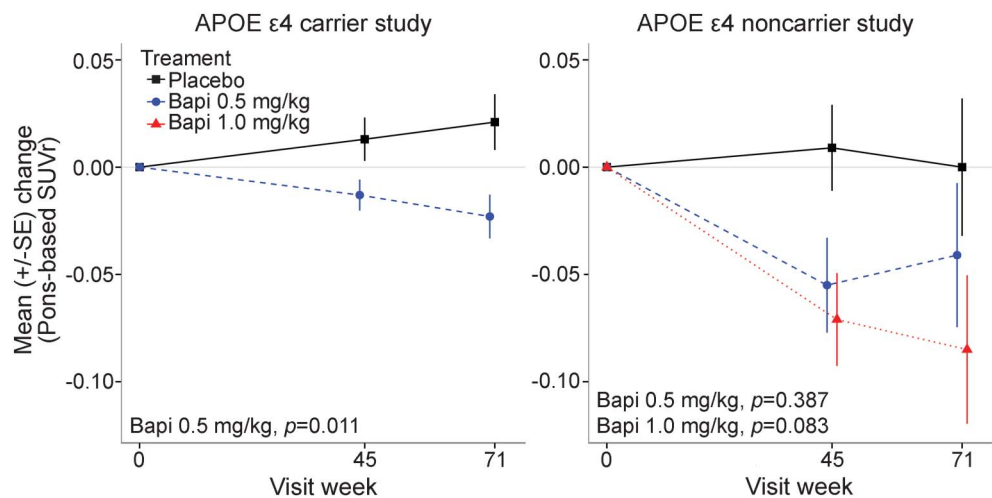
Similar to the results using the cerebellum as a reference region, a treatment difference in carriers was also observed when the pons was used as the reference region (carrier placebo/bapineuzumab [Bapi]: 40/75; noncarrier placebo/0.5 mg/kg/1.0 mg/kg: 15/12/12). SUVr = standardized uptake value ratio.

may also be influenced by one or a combination of factors including the small sample size and impact of technical variability that may have been by introduced by the use of multiple types of scanners in the study and noise from the reference region used in the analysis.[18]

Several studies evaluating AD therapies have incorporated amyloid PET imaging as an outcome measure. In the phenserine trial[19] and in the solanezumab trials,[16] no impact of therapy on brain amyloid by PET was observed. In trials with other antiamyloid therapies,[3,5,20] small to modest treatment reductions on brain amyloid by PET were observed. However, this was not accompanied by clinical benefit[5] or not reported.[20] Thus, a question remains as to whether the mechanism of amyloid removal by AD drugs has really been tested.[18–20]

The inability to include higher dose levels (limited by symptomatic ARIA), especially in the carriers, prevented evaluating the potential impact of greater amyloid removal on clinical outcome. Participant enrollment based on clinical criteria manifested in frequent amyloid negatives, especially in the noncarriers, resulting in the reduction of the number of analyzable scans. Although the reported analyses were prespecified, there was no statistical correction for multiple comparisons. Additionally, the pooled study results must be interpreted cautiously, since the 1.0 mg/kg group consisted only of noncarriers whereas the placebo group comprised both carriers and noncarriers.

In spite of the evidence of target engagement by bapineuzumab, no clinical benefit was evident in the phase 3 trials.[5] If Aβ plays a role in the development of AD, these findings raise questions about whether bapineuzumab was initiated early enough to affect the disease course, the exposure was sufficient, or the most pathologic Aβ species were targeted.

Comment:
Yet another "disconnect" between amyloid and Alzheimer disease?

Amyloid plaque pathology is a defining characteristic of Alzheimer disease (AD), and the amyloid cascade hypothesis remains a central focus of AD research. Yet at least a dozen treatment trials have achieved target engagement by reducing fibrillar amyloid or its production, but have shown no clinical benefit. The article by Liu et al.[1] shows that the monoclonal anti-Aβ antibody bapineuzumab diminished binding of ^{11}C–Pittsburgh compound B (PiB) in mild to moderate AD dementia, most notably in persons with *APOE* ε4.

The phase III bapineuzumab trials, however, failed to show treatment-related attenuation of cognitive or functional decline. The article by Liu et al. does not discuss that disconnect, perhaps because it is now all too familiar. The rationale usually offered for it is that the intervention was offered too late in the AD pathogenetic cascade.

Speculation is growing, however, regarding another explanation: that fibrillar amyloid (the target of PiB) does not cause the symptoms of AD dementia. Newer trials are testing whether anti-amyloid treatments can attenuate the progress of pre-clinical AD, either in cognitively normal elders with evidence of cerebral amyloidosis[2] or in those who harbor a pathogenetic *PSEN1* mutation.[3] Contemplation of the eventual results of these trials raises a serious question: just what would constitute compelling evidence that anti-amyloid treatments cannot stop the evolution of the AD pathogenic cascade? Indeed, a null result from the *PSEN1* trial would place the severest strain on the entire amyloid cascade hypothesis. The pharmaceutical industry has by now invested several billion dollars in anti-amyloid therapeutics. Karl Popper taught us that scientific discovery requires falsifiable hypotheses. Should we not be asking what could convince us that the anti-amyloid treatment emperor may have no clothes?[4]

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coordination. H.R. Brashear: study concept and design, acquisition of data, analysis and interpretation of data, drafting/revising manuscript for content, study supervision and coordination.

DISCLOSURE

E. Liu is or was an employee of Janssen Alzheimer Immunotherapy. M. Schmidt is an employee of Janssen Pharmaceutica. R. Margolin is or was an employee of Janssen Alzheimer Immunotherapy. R. Sperling has served as a consultant for Roche, Janssen, Lundbeck, Genentech, and Isis. She has received research support from Eli Lilly and Company and Janssen. R. Koeppe was a consultant to Johnson & Johnson, Avid, and Merck at the time the manuscript was developed. N. Mason has provided consultancy for Janssen Alzheimer Immunotherapy for the PiB portions of the 301/302 studies related to this manuscript. Dr. Mason has consulted for other pharmaceutical companies, including Elan and Johnson & Johnson. W. Klunk receives royalty payments from GE Healthcare for licensed PiB-PET technology, has served as a consultant to GE Healthcare and Janssen AI, and has received several grants from the NIH (AG025204, AG025516, AG028526, AG014449, AG005133, and AG012138). C. Mathis receives royalty payments from GE Healthcare for licensed PiB-PET technology. S. Salloway is a consultant to Janssen Alzheimer Immunotherapy, Avid/Lilly, GE Healthcare, AstraZeneca, Biogen, Roche, iPierian, Novartis, Merck, and Piramal, all involving under $5,000. Dr. Salloway's hospital receives research support for the conduct of clinical trials sponsored by Jansen 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 MR image 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, Pfizer, Sanofi, and Wyeth. Dr. Fox receives no personal compensation for the aforementioned activities. D. Hill is an employee of IXICO plc. Dr. Hill holds stock and share options in IXICO plc. Through IXICO, he has provided services to Pfizer, Janssen Alzheimer Immunotherapy, Bristol-Myers Squibb, Lilly, Teva, Roche, MedImmune, GlaxoSmithKline, Kyowa Hakko Kirin, Green Valley, Eisai, VirtualScopics, and Enkam. Dr. Hill holds non-study-related patents in image data management and image analysis. Also through IXICO, he has received research grant support from the European grant sources Innovative Medicines Initiative and FP7, also including in the UK the Technology Strategy Board and the Medical Research Council. A. Les is an employee of IXICO plc. P. Collins is or was an employee of Janssen Alzheimer Immunotherapy. K. Gregg is or was an employee of Janssen Alzheimer Immunotherapy. J. Di is or was an employee of Janssen Alzheimer Immunotherapy. Y. Lu reports no disclosures relevant to the manuscript. C. Tudor is or was an employee of Janssen Alzheimer Immunotherapy. B. Wyman is an employee of Pfizer. K. Booth is an employee of Pfizer. S. Broome is or was an employee of Janssen Alzheimer Immunotherapy. E. Yuen is or was an employee of Janssen Alzheimer Immunotherapy. M. Grundman was a paid consultant to Janssen Alzheimer Immunotherapy in the development of this manuscript and has consulted for other pharmaceutical companies, including Adamas, Acumen, ALSP, AstraZeneca, Avid, Biogen Idec, Bristol-Myers Squibb, Elan,

Johnson & Johnson, Intellect Neurosciences, iPierian, Lilly, MedImmune, NeuroGenetic Pharmaceuticals, NeuroPhage, Nutricia, Phloronol, Prothena, Probiodrug, QR Pharma, and Teva. H. Brashear is or was an employee of Janssen Alzheimer Immunotherapy. Go to Neurology.org for full disclosures.

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