**Summary**

**Background** Carbon-11-labelled Pittsburgh compound B (¹¹C-PiB) PET is a marker of cortical fibrillar amyloid-β load in vivo. We used ¹¹C-PiB PET to investigate whether bapineuzumab, a humanised anti-amyloid-β monoclonal antibody, would reduce cortical fibrillar amyloid-β load in patients with Alzheimer’s disease.

**Methods** Patients with mild-to-moderate Alzheimer’s disease were randomly assigned to receive intravenous bapineuzumab or placebo in a ratio of seven to three in three ascending dose groups (0·5, 1·0, or 2·0 mg/kg). Each dose group was enrolled after safety review of the previous group. Randomisation was by interactive voice response system; masking was achieved with numbered kit allocation. Patients, investigators, study site personnel, sponsor staff, and carers were masked to treatment. Patients received up to six infusions, 13 weeks apart, and had ¹¹C-PiB PET scans at baseline and at weeks 20, 45, and 78. The primary outcome was the difference between the pooled bapineuzumab group and the pooled placebo group in mean change from screening to week 78 in ¹¹C-PiB cortical to cerebellar retention ratio averaged across six cortical regions of interest. Analysis was by modified intention to treat. This study is registered with EudraCT, number 2004-004120-12; ISRCTN17517446.

**Findings** 28 patients were assigned to bapineuzumab (n=20) or placebo (n=8). 19 patients in the bapineuzumab group and seven in the placebo group were included in the modified intention-to-treat analysis. Estimated mean ¹¹C-PiB retention ratio change from baseline to week 78 was –0·09 (95% CI –0·16 to –0·02; p=0·014) in the bapineuzumab group and 0·15 (95% CI 0·02 to 0·28; p=0·022) in the placebo group. Estimated mean difference in ¹¹C-PiB retention ratio change from baseline to week 78 between the bapineuzumab group and the placebo group was –0·24 (95% CI –0·39 to –0·09; p=0·003). Differences between the bapineuzumab group and the placebo group in the individual regions of interest were similar to the overall mean difference. Adverse events were typically mild to moderate in severity and transient. Two patients in the 2·0 mg/kg bapineuzumab group had transient cerebral vasogenic oedema.

**Interpretation** Treatment with bapineuzumab for 78 weeks reduced cortical ¹¹C-PiB retention compared with both baseline and placebo. ¹¹C-PiB PET seems to be useful in assessing the effects of potential Alzheimer’s disease treatments on cortical fibrillar amyloid-β load in vivo.

**Funding** Elan Pharmaceuticals and Wyeth Research.

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**11C-PiB PET assessment of change in fibrillar amyloid-β load in patients with Alzheimer’s disease treated with bapineuzumab: a phase 2, double-blind, placebo-controlled, ascending-dose study**


Lancet Neurol 2010; 9: 363–72

Published Online March 1, 2010
DOI:10.1016/S1474-4422(10)70043-0

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We aimed to investigate whether bapineuzumab-related changes in cortical amyloid-β load could be measured in vivo by use of ¹¹C-PiB PET imaging.

**Methods**

**Patients**

We did a phase 2, multicentre, randomised, double-blind, placebo-controlled, ascending-dose study at three clinical sites (two in the UK and one in Finland) between August, 2005, and January, 2009.

Eligible patients were aged 50–80 years inclusive, met NINCDS-ADRDA criteria for probable Alzheimer’s disease,11 and had amyloid-β loads in the range expected for patients with Alzheimer’s disease, defined as ¹¹C-PiB PET retention ratios relative to the cerebellum of 1·5 or more in at least three brain regions among the anterior cingulate, posterior cingulate, frontal, temporal, and parietal cortices. Additional inclusion criteria were MRI consistent with Alzheimer’s disease, a mini-mental state examination (MMSE) score of 18–26, and a Rosen modified Hachinski ischaemic score of at least 4.13 Patients were excluded if they had clinically significant neurological disease other than Alzheimer’s disease; had a major psychiatric disorder; had a history of stroke or seizures; had a Hamilton rating scale for depression score greater than 12;14 or were currently taking anticonvulsants, antiparkinsonian, anticoagulant, or narcotic drugs, recent immunosuppressive or cancer chemotherapy drugs, or cognitive enhancers other than acetylcholinesterase inhibitors or memantine at a stable dose for at least 120 days before screening.

The study was approved by the local independent ethics board at each site, and each patient (or a legally authorised representative) gave written informed consent before enrolment.

**Randomisation and masking**

Patients were randomly assigned to receive either intravenous bapineuzumab or placebo in one of three dose groups (0·5, 1·0, or 2·0 mg/kg). Patients who completed the screening phase and met all inclusion criteria were eligible for randomisation. An interactive voice response system (IVRS) vendor generated the treatment assignments, and visit-specific blinded study drug kits were dispensed by the IVRS. The IVRS vendor personnel had no further contact with study site staff, patients, or carers. On the basis of the information provided by the IVRS vendor, a masked pharmacist or dispenser took the study drug kit with the allocated kit number and prepared the infusion. During the study, patients, investigators (both image analysts and clinical assessors), study site personnel, and sponsor staff were masked to treatment.

A four-member independent safety monitoring committee assessed the safety of treatment throughout the trial. The 0·5 mg/kg dose group was first to be enrolled. Each subsequent dose group was enrolled after the safety monitoring committee reviewed safety in the preceding groups.

**Procedures**

Patients received study drug as a 1 h intravenous infusion every 13 weeks for up to six infusions. Each patient had ¹¹C-PiB PET, fluorine-18-labelled-fluorodeoxyglucose (¹⁸F-FDG) PET, clinical assessments of cognition and function (activities of daily living), volumetric and clinical MRI, and clinical laboratory investigations (eg, haematology). CSF amyloid beta and tau concentrations were measured in a subset of patients. Final assessment was at week 78.

Imaging was done at two PET sites (one in the UK and one in Finland). Details of the synthesis of ¹¹C-PiB and PiB PET data collection have been described.10 Briefly, all ¹¹C-PiB images were obtained by use of an ECAT EXACT HR+ scanner (Siemens, Erlangen, Germany) after an attenuation scan that preceded an intravenous bolus of about 370 MBq ¹¹C-PiB (specific activity ≥10 GBq/μmol at injection). Images were obtained in 32 frames over 90 min. Cortex to cerebellar ratio images of ¹¹C-PiB retention were generated at a single site (Hammersmith Imanet, GE Healthcare, London, UK) by use of data from 60–90 min after injection.¹¹C-PiB PET images were co-registered to each patient’s MRI, which was normalised into standard stereotactic space (Montreal Neurological Institute, Quebec, Canada). A probabilistic brain atlas was used to create a standard template of regions of

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**Figure 1: Trial profile**

1 had no post-baseline PET data
2 withdrew
2 had adverse events
19 included in PiB PET analysis (modified intention-to-treat population)

25 failed screening
23 did not meet inclusion criteria
1 withdrew consent
1 other reasons*

8 assigned to receive placebo (safety population)
3 to 0·5 mg/kg
3 to 1·0 mg/kg
2 to 2·0 mg/kg

20 assigned to receive bapineuzumab (safety population)
7 to 0·5 mg/kg
7 to 1·0 mg/kg
6 to 2·0 mg/kg

53 assessed for eligibility
20 randomised

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*Patient excluded because enrolment in 2·0 mg/kg group was ended by the sponsor. 115 of 20 patients had PET data at week 78: two withdrew and scans were not completed in three. Five of eight patients had PET data at week 78: two withdrew and scans were not completed in one. PiB=Pittsburgh compound B.
interest for sampling segmented grey matter regions.⁰¹ Cortex to cerebellum ratios are unitless, and a ratio of 1:0 indicates no specific ¹¹C-PiB retention and should be accounted for in calculations of percent change. For example, a decrease from 2:0 to 1:8 ratio units would represent a 20%-0% decrease in specific ¹¹C-PiB retention (ie, [2·0−1·8]/[2·0–1·0]). For analysis, six predefined cortical regions of interest were included: the anterior cingulate, posterior cingulate, frontal, temporal, parietal, and occipital cortices. The mean of all six regions of interest was also calculated. ¹¹C-PiB PET scans were done at screening and at weeks 20, 45, and 78.

Parametric images of regional cerebral glucose metabolism relative to the brainstem were made from brain ¹⁸F-FDG time activity curves 35–55 min after injection of the tracer. These parametric images were transformed into Montreal Neurological Institute stereotaxic space, and a probabilistic atlas was used to define six cortical regions of interest and their mean at screening and at week 78.

The Alzheimer’s disease assessment scale-cognitive subscale (ADAS-cog), neurocognitive test battery, and MMSE (range 0–30) were done about every 3 months. The clinical dementia rating sum of boxes (range 0–18)²⁰ and Neuropsychiatric inventory ⁸·¹¹ (⁸·⁰¹) ⁵·²⁹ (⁴·²⁷) were done every 3 months. In patients who consented to having lumbar puncture, CSF was taken before treatment and at week 52. CSF biomarkers were measured by sandwich ELISA for total tau, phosphorylated tau, and amyloid β₄₂ (with the 4G8 antibody replacing 3D6 to measure amyloid β₄₂). Volumetric and safety MRI scans were done before treatment, at week 6, and then at 13-week intervals until week 71. MRI outcomes included changes in brain and ventricular volumes evaluated using the brain and ventricular boundary shift integral from baseline.²⁵

To investigate whether bapineuzumab competes with PiB binding, we did an assay to measure ¹¹H-PiB binding to amyloid-β fibrils and Alzheimer’s disease brain homogenates in the presence of bapineuzumab. By use of previously described procedures,²⁶,²⁷ the appropriate concentrations of bapineuzumab in phosphate-buffered saline (PBS, pH 7·0) were combined with ¹¹H-PiB (67 Ci/mmol; about 1 nM) in a volume of 900 mL of PBS. The assay was started by addition of either 100 mL of amyloid-β fibril stock solution (final nominal concentration of 200 nM amyloid β) or 100 mL of Alzheimer’s disease brain homogenate (final concentration of 100 µg tissue per mL) prepared as described.²⁸,²⁹ After incubation for 60 min at room temperature, the binding mixture was filtered through a Whatman GF/B glass filter via a Brandel M-24R cell harvester (Gaithersburg, MD, USA) and rapidly washed twice with 3 mL PBS for amyloid-β fibrils and five times for Alzheimer’s disease brain homogenates, and measured the amount of tissue and fibrils with bound ¹¹H-PiB.

**Statistical analysis**

We planned to enrol 30 patients (ten per dose group, with patients in each dose group receiving bapineuzumab or placebo in a seven to three ratio). On the basis of previously reported standardised uptake values,³ we estimated that with this sample size there would be greater than 97% power to detect a treatment difference of 0·25 in ¹¹C-PiB retention between pooled bapineuzumab and pooled placebo groups in the change from screening to week 78, using a two-sided t test at a significance level of 0·05. The study was not powered to measure efficacy for clinical or other biomarker outcomes.

The prespecified primary analysis compared the pooled bapineuzumab and pooled placebo groups at week 78 by use of the mixed model for repeated measures. The primary endpoint was the change from screening to weeks 20, 45, and 78 in the ¹¹C-PiB mean cortical to cerebellar retention ratio across the six predefined cortical regions of interest. The explanatory variables were treatment group, screening ¹¹C-PiB PET...
value as a continuous covariate, baseline MMSE category (high [22–26] vs low [18–21]), visit week (a categorical factor), and the interaction between treatment and visit week. The covariance matrix was chosen from a prespecified set on the basis of Akaike’s information criterion. The primary analysis was a two-sided test of the week 78 least-squares mean difference. Analysis was by modified intention to treat, predefined as all randomised patients who received any amount of study drug and who had a screening and at least one valid PET scan after baseline. The six $^{11}$C-PiB PET regions of interest were analysed with the same method as for the overall $^{11}$C-PiB PET mean.

The change from screening in the $^{18}$F-FDG PET mean was analysed by use of ANCOVA with model terms for treatment (pooled bapineuzumab vs pooled placebo), screening value, and baseline MMSE category. MRI and clinical endpoints were analysed with the same method as for $^{11}$C-PiB PET mean, except that the model for brain boundary shift integral included baseline whole brain volume as a covariate and the model for ventricular boundary shift integral included baseline ventricular volume as a covariate. CSF variables were analysed with the same ANCOVA method as for $^{18}$F-FDG PET.

Because of apparent differences between the bapineuzumab group and the placebo group on some baseline assessments (eg, neuropsychological test battery, clinical dementia rating sum of boxes, and mean $^{11}$C-PiB PET) we adjusted for these imbalances in additional post-hoc analyses: the mixed model for repeated measures and ANCOVA analyses were repeated without the screening and baseline covariates but with the addition of model terms for baseline neuropsychological test battery, clinical dementia rating sum of boxes, and $^{11}$C-PiB mean and, in the mixed model for repeated measures, the corresponding covariate-by-visit interactions. Exploratory analyses were not adjusted for multiple comparisons.

This study is registered, EudraCT number 2004-004120-12; ISRCTN17517446.

**Role of the funding source**

Employees of both sponsors were involved in the study design, data collection, data analysis, and interpretation of data, and in the development and submission of this manuscript. All authors had access to all study data and shared responsibility for the decision to submit the manuscript for publication.

**Results**

Of 53 screened patients, 28 were randomly assigned (20 bapineuzumab vs eight placebo; ten in the 0·5 mg/kg group, ten in the 1·0 mg/kg group, and eight in the 2·0 mg/kg group; figure 1). The sponsor stopped enrolment in the 2·0 mg/kg group after a greater frequency of patients with cerebral vasogenic oedema after treatment with this dose was reported from...
another study. Eight patients did not meet the inclusion criteria because of low $^{11}$C-PiB retention. 15 patients failed to meet other inclusion criteria, and two did not complete enrolment. All patients who were randomly assigned received at least one dose of bapineuzumab or placebo and were included in the analysis of safety data (safety population). Among those allocated to treatment, 26 patients (19 in the bapineuzumab group and seven in the placebo group) had $^{11}$C-PiB assessment at baseline and at least once thereafter and were included in the modified-intention-to-treat population. 18 patients in the bapineuzumab group and six in the placebo group were assessed at week 78. 15 patients in the bapineuzumab group and five in the placebo group had $^{11}$C-PiB assessment at week 78.

Table 1 shows baseline characteristics. A number of baseline characteristics seemed to differ between treatment groups: the mean $^{11}$C-PiB mean retention ratio ($p=0·058$; anterior cingulate cortex $p=0·029$ and frontal cortex $p=0·040$) and mean clinical dementia rating sum of boxes score were higher ($p=0·007$), whereas the mean neuropsychological test battery score was lower ($p=0·040$) in the bapineuzumab group than in the placebo group. Five of seven patients in the placebo group were in the high MMSE category (22–26) compared with seven of 19 in the bapineuzumab group.

Estimated mean $^{11}$C-PiB retention ratio decreased by −0·02 in the bapineuzumab group (95% CI −0·16 to −0·02; $p=0·014$) and increased by 0·15 in the placebo group (95% CI 0·02 to 0·28; $p=0·022$) from baseline to week 78 (estimated difference −0·24 [95% CI −0·39 to −0·09], $p=0·003$; table 2). The estimated treatment difference between the bapineuzumab group and the placebo group increased over time ($p=0·06$ for treatment-by-visit interaction; figure 2). Across the six regions of interest, changes from baseline to week 78 showed reductions in $^{11}$C-PiB retention ratio in the bapineuzumab group and increases in the placebo group (table 2). The difference in the mean $^{11}$C-PiB retention ratio between the bapineuzumab group and the placebo group was −0·24 for the 0·5mg/kg dose group ($p=0·009$), −0·18 for the 1·0 mg/kg dose group ($p=0·051$), and −0·29 for the 2·0 mg/kg dose group ($p=0·003$). Figure 3 shows $^{11}$C-PiB PET retention for individual patients by treatment group at baseline and at their last available visit, as well as the change from baseline to last available visit. Figure 4 shows $^{11}$C-PiB scans for individual patients before and after 78 weeks of treatment with bapineuzumab or placebo.

The estimated mean $^{11}$C-PiB treatment difference between the bapineuzumab group and placebo group was −0·25 (95% CI −0·47 to −0·03) after adjusting for baseline neuropsychological test battery score, clinical dementia rating sum of boxes score, and mean $^{11}$C-PiB retention ($p=0·025$; table 3). The mean $^{11}$C-PiB change from
baseline to week 78 in the bapineuzumab group was –0·08 for nine patients with the apolipoprotein E (APOE) ε4 allele and –0·10 for six patients without. No treatment differences were noted on the clinical, ¹⁸F-FDG PET, MRI, or CSF endpoints after adjusting for baseline imbalances on the neuropsychological test battery, clinical dementia rating sum of boxes, and ¹¹C-PiB (table 3).

Bapineuzumab does not compete with ³H-PiB binding to Alzheimer’s disease brain homogenates or synthetic amyloid-β fibrils at concentrations of up to 20 000 ng/mL (webappendix).

Treatment-emergent adverse events were reported in 19 of 20 patients in the bapineuzumab group and in eight of eight patients in the placebo group. Adverse events were typically mild to moderate in severity and transient. Adverse events that were reported in at least 10% of patients in the bapineuzumab group included headache, nasopharyngitis, fatigue, diarrhoea, urinary tract infection, falls, abrasions, and muscle spasms. Serious adverse events were reported in four of 20 patients in the bapineuzumab group and in three of eight in the placebo group. With the exception of cerebral vasogenic oedema, adverse events did not seem to be dose-related. Two patients in the 2·0 mg/kg bapineuzumab group had cerebral vasogenic oedema, both of whom were APOE ε4 carriers (one homozygous and one heterozygous). Both patients were asymptomatic (the events were identified during MRI surveillance) and each patient had received one dose of bapineuzumab before onset. Vasogenic oedema resolved after the patients discontinued treatment. One patient with cerebral vasogenic oedema had a follow-up ¹¹C-PiB scan. No deaths were reported in the entire study population.

**Discussion**

There was a significant difference in change from baseline in the ¹¹C-PiB PET mean retention from six targeted regions of interest in patients in the bapineuzumab group compared with those in the placebo group. A reduction in ¹¹C-PiB retention relative to baseline was noted for the bapineuzumab group, while an increase was observed in the placebo group. Other recent studies have also reported small increases in ¹¹C-PiB retention over time in patients with Alzheimer’s disease,

The difference in ¹¹C-PiB retention between the bapineuzumab and placebo groups was similar for each of the three doses tested, and the treatment difference increased over time. Although these analyses by region are consistent with the primary analysis that averaged all six regions of interest, no multiplicity adjustment was done, and confirmation of these findings in other studies is warranted.

The –0·09 ratio units for bapineuzumab over 78 weeks represents an 8·5% decline from the baseline value of 2·06, whereas the 0·15 ratio units for placebo represents...
a 16.9% increase over the baseline value of 1.89. By use of this percentage approach, one can estimate that bapineuzumab treatment was associated with an approximate 25% reduction in cortical fibrillar amyloid $\beta$ over 78 weeks compared with placebo. N-terminal antibodies bind amyloid-$\beta$ oligomers as well as diffuse and compact plaques, whereas PiB binds only fibrillar amyloid $\beta$ and binds diffuse plaques less strongly than compact plaques. $^{6,7}$ $^{11}$C-PiB might underestimate the effect of bapineuzumab on total amyloid-$\beta$ burden. Consistent with the increasing treatment difference in $^{11}$C-PiB retention over time, greater differences might also be possible with extended treatment.

This trial had several limitations. The sequential recruitment of small groups of patients to ascending doses of bapineuzumab limited the capacity to assess potential dose-response effects. There were baseline imbalances between the two treatment groups on some measures (eg, disease severity was greater in the bapineuzumab group than the placebo group). After adjustment for imbalances in baseline $^{11}$C-PiB PET retention and clinical scores, the difference in $^{11}$C-PiB PET retention between the bapineuzumab group and the placebo group remained, whereas no differences were noted on the clinical or other biomarker outcomes.

Whether a reduction in cortical fibrillar amyloid $\beta$ leads to clinical benefit has not been established. A previous phase 2 trial found preliminary evidence for clinical efficacy in patients with Alzheimer’s disease who completed a treatment course of bapineuzumab over 78 weeks. $^7$ Treatment differences in that trial

| Table 3: Treatment differences with and without adjustment for potential baseline imbalances |
|--------------------------------------------------|---------------------|---------------------|
| $^{11}$C-PiB endpoints                         | $^{11}$C-PiB mean  | $^{11}$C-PiB mean  |
|                                                 | $^{11}$C-PiB mean  | $^{11}$C-PiB mean  |
| Anterior cingulate cortex                      | 0.003              | 0.005              |
| Posterior cingulate cortex                     | 0.014              | 0.014              |
| Frontal cortex                                 | 0.006              | 0.006              |
| Temporal cortex                                | 0.002              | 0.002              |
| Parietal cortex                                | 0.004              | 0.004              |
| Occipital cortex                               | 0.001              | 0.001              |
| Clinical endpoints                             | ADAS-cog 11-item   | ADAS-cog 11-item   |
|                                                 | 0.081              | 0.081              |
| Discrepancy for dementia                       | 0.910              | 0.910              |
| Clinical dementia rating sum of boxes          | 0.799              | 0.799              |
| Neuropsychological test battery                | 0.676              | 0.676              |
| Neuropsychiatric inventory                     | 0.889              | 0.889              |
| Mini-mental state exam                         | 0.178              | 0.178              |
| Biomarker endpoints                            | $^{18}$F-FDG mean  | $^{18}$F-FDG mean  |
|                                                 | 0.796              | 0.796              |
| Brain BSI                                      | 0.914              | 0.914              |
| Ventricular BSI                                | 0.080              | 0.080              |
| CSF amyloid 42                                 | 0.745              | 0.745              |
| CSF tau                                        | 0.257              | 0.257              |
| CSF phosphorylated tau                         | 0.081              | 0.081              |

For $^{11}$C-PiB endpoints (modified intention-to-treat analysis), negative treatment differences suggest less PiB retention for bapineuzumab; for clinical endpoints, positive treatment differences favour bapineuzumab (owing to conventions adopted for calculating change from baseline to represent improvement). A negative treatment difference for brain BSI (modified intention-to-treat analysis) suggests less brain volume loss in the bapineuzumab group compared with the placebo group. A positive treatment difference for ventricular BSI (modified intention-to-treat analysis) indicates a greater ventricular volume increase in the bapineuzumab group compared with the placebo group. For $^{18}$F-FDG mean (on the basis of available data at week 78: bapineuzumab n=17, placebo n=5), a positive value suggests greater $^{18}$F-FDG retention compared with baseline for the bapineuzumab group compared with the placebo group. For biomarker variables (on the basis of available CSF data at week 52: bapineuzumab n=7, placebo n=4), negative treatment differences for CSF tau and phosphorylated tau suggest greater reduction at week 52 relative to baseline in the bapineuzumab group compared with the placebo group, and positive treatment differences for CSF amyloid 42 suggest an increase relative to baseline in the bapineuzumab group compared with the placebo group. PiB=Pittsburgh compound B. ADAS-cog=Alzheimer’s disease assessment scale-cognitive subscale. $^{18}$F-FDG=fluorine-18-labelled-fluorodeoxyglucose. BSI=boundary shift integral.
increased over time, consistent with the time course of reduced $^{11}$C-PiB retention observed in this trial (figure 2). A previous study of patients immunised with the prototype amyloid-β vaccine AN1792 reported that some antibody responders progressed clinically despite evidence of reduced plaque burden at autopsy. Other studies, however, reported better performance on some clinical measures in antibody responders. The present study was not powered to assess clinical efficacy or other biomarker outcomes, and no significant differences on these outcomes were observed after adjusting for baseline imbalances; however, large, adequately powered phase 3 trials are underway to further investigate the clinical efficacy of bapineuzumab and its effects on imaging and CSF biomarkers. The number of patients with CSF data in this trial was low, and definitive conclusions with respect to the effects of bapineuzumab on CSF amyloid-β load cannot be made until larger studies are completed. Nevertheless, because of the complex equilibrium between fibrillar plaque and oligomeric and monomeric amyloid β in the brain, changes in cortical fibrillar amyloid β might not be directly or immediately associated with changes in CSF amyloid-β concentrations. The phase 3 programme aims to confirm the $^{11}$C-PiB PET findings reported here and to explore the relationship of clinical and biomarker outcomes with $^{11}$C-PiB retention.

Consistent with the current study, reversible cerebral vasogenic oedema was the main safety concern identified in the previous phase 2 trial, in which there was an increased incidence of vasogenic oedema at higher doses of bapineuzumab and in $APOE$ ε4 carriers.

This trial has potential implications for interventional studies seeking to prevent or alter the clinical course of Alzheimer’s disease. Monitoring of the effects of anti-amyloid-β drugs on amyloid-β deposition might be possible with radiotracers that bind to amyloid β in patients with Alzheimer’s disease or in those at risk before the onset of clinical decline. This technique offers the opportunity to test more directly the amyloid-β hypothesis by confirming the ability of a particular drug to reduce or prevent amyloid-β accumulation and to assess the effect this has on clinical outcomes.

**Contributors**
JOR, DJB, EL, RBl, MK, and MG designed the study, JOR, MNR, EL, RBl, and MG collected the data, DJB, NCF, AAO, SRMCh, EL, MK, DS, RBl, and MG analysed the data. NCF, RBu, WEK, CAM, DS, and RBl interpreted the data. JOR, DJB, MNR, RBu, MK, and MG wrote the manuscript. JOR, RJB, RBl, WEK, CAM, KB, AAO, MK, and RBl revised the manuscript. NCF, WEK, CAM, MK, and DS edited the paper. WEK and CAM supervised the in vitro binding assay experiments with bapineuzumab and $^{1}H$-PiB. KB did the CSF analysis. JB was a neuroradiologist consultant and central image reviewer. KMG did the statistical analysis.

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**Safety monitoring committee**
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**Conflicts of interest**
JOR’s institution received study funding through a research contract with Elan Pharmaceuticals and has received funding from Elan Pharmaceuticals through a research contract for which JOR was the local primary investigator. JOR has served as medical adviser for H Lundbeck and Boehringer-Ingelheim. DJB is a part-time employee of Hammersmith Imanet (GE Healthcare), which received funding from Elan Pharmaceuticals for PET scans. DJB has received funding from Elan Pharmaceuticals for travel and accommodation related to a PET expert meeting. MNR’s institution received grant funding from Wyeth and Elan Pharmaceuticals to do this clinical trial and honoraria to participate on safety monitoring committees for ongoing bapineuzumab clinical trials. MNR is Director of Dementias and Neurodegenerative Diseases Research Network (DeNDRoN). NCF has received funding from the Alzheimer’s Research Forum for participation on the Alzforum Scientific Advisory Board. NCF’s institution has received funding for consultant work at an article analysis meetings for Abbott Laboratories, Lundbeck, GE Healthcare, Elan Pharmaceuticals, Eli Lilly, Eisai, Wyeth Pharmaceuticals, Eli Lilly, Eisai, Wyeth, and Sanofi-Aventis. NCF has received funding for GE Healthcare for advisory board participation. NCF’s institute has received funding from the Movement Disorders Society and American Neurological Association for NCF participating as a speaker at a 2009 meeting, and from Elan and Wyeth Pharmaceuticals for advisory board participation. NCF has a patent pending from QA Box which might accrue future revenue. NCF’s institute has received royalties for Medical Image Display and Analysis Software. NCF has received reimbursement for travel expenses from the Movement Disorders Society and the American Neurological Association related to attendance and speaking at meetings. His institution has received payment for trial supports for contracted image analysis research from GlaxoSmithKline, Elan Pharmaceuticals, Lundbeck, Sanofi-Aventis, IXICO, and Pfizer. RBl has received honoraria for consulting services provided to Novartis, Pfizer, Johnson and Johnson, Myriad, Lundbeck, Eisai, Merck, and Abbott within the past 10 years. Time spent on these projects is reimbursed to his institution (part of Avon and Wiltshire Mental Health Partnership NHS Trust) by the Healthcare Commission. A research grant was provided by Elan Pharmaceuticals to RBl’s institution, AON and Wiltshire Mental Health Partnership Trust. RBl has received payment for travel to conferences from Novartis, Pfizer, Johnson and Johnson, Myriad, Lundbeck, and Eisai within the past 10 years. WEK received consulting fees and honoraria for attending and participating in a PET advisers meeting with Elan Pharmaceuticals and support for airfare and accommodation for scientific advisors meeting with Elan Pharmaceuticals. WEK received payment for being a consultant on the scientific advisory board for Neuroptix. WEK’s institution received grant funding from GE Healthcare from 2002 to 2007, and receives patent licences and royalties from GE Healthcare. WEK receives 10% licence payment and royalties as a co-inventor of Pittsburgh compound B from GE Healthcare. WEK received 3000 shares of Neuroptix for serving on the scientific advisory board. WEK also received airfare and accommodation reimbursement from Elan Pharmaceuticals for travel related to any scientific advisory meeting. CAM has received consulting fees for participating on scientific advisory boards for Neuroptix and from Elan and Wyeth Pharmaceuticals. His institution has received grant funding from GE Healthcare from 2002 to 2007, and from Neuroptix from 2007 to present, and receives patent licence payments and royalties from GE Healthcare. CAM receives 10% licence payment and royalties as a co-inventor of Pittsburgh compound B from GE Healthcare. CAM received 3000 shares of Neuroptix for serving on the scientific advisory board, and received airfare and accommodation reimbursement from Elan Pharmaceuticals for travel related to a scientific advisory meeting. KB received payment for once serving as a member of an advisory board for Elan Pharmaceuticals. JB received payment for serving as a neuroradiological consultant to Synarc, contracted by Janssen.
Alzheimer Immunotherapy. JB also received payment for consulting with Janssen Alzheimer Immunotherapy for non-clinical research activities. AAO received consulting fees and honoraria from Elan Pharmaceuticals for image analysis services. AAO’s salary is supported by a grant from the Alzheimer’s Research Trust and any travel, accommodation and conference-related expenses while working as an Alzheimer’s Research Trust associate are reimbursed by the Alzheimer’s Research Trust. SRMMdL and her institution received consulting fees and honoraria from Elan Pharmaceuticals for PET scans and analysis. EL is a former employee of Elan Pharmaceuticals and continues to receive stock options from Elan Pharmaceuticals. EL receives travel and accommodation expense reimbursement from Janssen Alzheimer Immunotherapy. MK is a former employee of Elan Pharmaceuticals and received consulting fees and support for travel from Elan Pharmaceuticals when separately serving as a consultant and attending data review sessions. MK received payment for serving as a consultant in writing and reviewing this manuscript. When employed by Elan Pharmaceuticals, MK contributed to the writing and editing of the study protocol, monitored part of the study and reviewed ongoing safety assessments for this study. As a former employee, he also received stock options from Elan Pharmaceuticals. KMG is a former employee of Elan Pharmaceuticals. DS holds stock and stock options in Elan Pharmaceuticals. RBJ receives stock and stock options with Pfizer. RBJ is a former employee of Wyeth Research (which was acquired by Pfizer in October, 2009). MG holds stock and stock options in Elan Pharmaceuticals.

Acknowledgments

This study was sponsored by Elan Pharmaceuticals, Inc (Janssen Alzheimer Immunotherapy acquired the Alzheimer Immunotherapy Program from Elan in September, 2009) and Wyeth Research (which was acquired by Pfizer in October, 2009). We acknowledge the following individuals for their assistance: Cherry Lucas, Jonathan Lowery, Margaret Cooney, and Sheila O’Mahony for study management; Kristen Morris for pharmacovigilance; Rezi Zawadski, Lorna Fang, and Jenny Wei for statistical analyses; John Baer and Kay Jing for clinical study summaries; and Shona Clegg for MRI volumetric analyses. We thank the patients and their caregivers for their dedication to and participation in the study.

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