Amyloid-related imaging abnormalities in patients with Alzheimer’s disease treated with bapineuzumab: a retrospective analysis


Summary

Background Amyloid-related imaging abnormalities (ARIA) have been reported in patients with Alzheimer’s disease treated with bapineuzumab, a humanised monoclonal antibody against amyloid β. ARIA include MRI signal abnormalities suggestive of vasogenic oedema and sulcal effusions (ARIA-E) and microhaemorrhages and haemosiderin deposits (ARIA-H). Our aim was to investigate the incidence of ARIA during treatment with bapineuzumab, and evaluate associated risk factors.

Methods Two neuroradiologists independently reviewed 2572 fluid-attenuated inversion recovery (FLAIR) MRI scans from 262 participants in two phase 2 studies of bapineuzumab and an open-label extension study. Readers were masked to the patient’s treatment, APOE ε4 genotype, medical history, and demographics. Patients were included in risk analyses if they had no evidence of ARIA-E in their pre-treatment MRI, had received bapineuzumab, and had at least one MRI scan after treatment. We used Kaplan-Meier survival analysis to examine the distribution of incident ARIA-E from the start of bapineuzumab treatment and proportional hazards regression models to assess risk factors associated with ARIA.

Findings 210 patients were included in the risk analyses. 36 patients (17%) developed ARIA-E during treatment with bapineuzumab; 15 of these ARIA-E cases (42%) had not been detected previously. 28 of these patients (78%) did not report associated symptoms. Adverse events, reported in eight symptomatic patients, included headache, confusion, and neuropsychiatric and gastrointestinal symptoms. Incident ARIA-E occurred in 17 of the patients with ARIA-E (47%), compared with seven of 177 (4%) patients without ARIA-E. 13 of the 15 patients in whom ARIA-E were detected in our study received additional treatment infusions while ARIA-E were present, without any associated symptoms. Occurrence of ARIA-E increased with bapineuzumab dose (hazard ratio [HR] 2.24 per 1 mg/kg increase in dose, 95% CI 1.40–3.62; p=0.0008) and presence of APOE ε4 alleles (HR 2.55 per allele, 95% CI 1.57–4.12; p=0.0001).

Interpretation ARIA consist of a spectrum of imaging findings with variable clinical correlates, and some patients with ARIA-E remain asymptomatic even if treatment is continued. The increased risk of ARIA among APOE ε4 carriers, its association with high bapineuzumab dose, and its timeframe in relation to dosing suggest an association between ARIA and alterations in vascular amyloid burden.

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Introduction Numerous clinical trials are investigating active or passive immunotherapeutic approaches to reduce cerebral amyloid-β burden as treatments for Alzheimer’s disease.1 1 Several of these studies have reported treatment-related abnormalities in brain images, but the pathophysiology underlying these changes is uncertain.1 1 Furthermore, because these imaging abnormalities can be clinically silent, their exact incidence and the spectrum of associated clinical features is unclear.

Imaging abnormalities associated with immunotherapy were first noted in a phase 1 study of bapineuzumab,1 a humanised monoclonal antibody against β amyloid, and then in phase 2 bapineuzumab studies.2 2 The MRI abnormalities, seen in T2*-weighted, fluid-attenuated inversion recovery (FLAIR) sequences, were initially referred to as vasogenic oedema.3 As additional cases were identified in subsequent trials, it became clear that a spectrum of imaging alterations associated with amyloid-modifying treatments existed. An expert workgroup has suggested the use of an umbrella term—amyloid-related imaging abnormalities (ARIA)—which includes FLAIR signal abnormalities thought to represent parenchymal vasogenic oedema and sulcal effusions (ARIA-E), as well as abnormalities detectable on T2*-weighted gradient echo sequences that are thought to represent microhaemorrhages and haemosiderosis (ARIA-H).

This report focuses on incident ARIA in the setting of clinical trials of bapineuzumab treatment; however, the findings could also have implications for other anti-amyloid therapies. Because the original protocols for
these trials included only MRI readings done by local radiologists, who might have had limited previous experience with ARIA, some cases of ARIA might have been missed. Therefore, we did a systematic, central review of all MRI data from these studies to assess the incidence of ARIA during bapineuzumab treatment, and their associated risk factors and clinical characteristics.

Methods
Participants and procedures
We reviewed all MRI scans performed before Feb 1, 2009, in two phase 2 bapineuzumab clinical trials (study 201 and study 202) and the associated ongoing open-label extension study (study 251; registered at ClinicalTrials.gov, number NCT00606476). We used several procedures to ensure maximum sensitivity for ARIA detection. Two neuroradiologists (DT and a contracted reader), who had full access to all MRI scans at all timepoints, retrospectively reviewed the scans for each participant; they were masked to the participant’s assigned therapy, APOE ε4 genotype, medical history, and demographics. The scans were first read independently by each reader, then any differences between readings were discussed and resolved by consensus between the two readers.

Studies 201 and 202 were multicentre, double-blinded, randomised, placebo-controlled, ascending-dose cohort trials.1,2 Each study lasted for 18 months and included six infusions, 13 weeks apart. Study 251 is an ongoing extension study into which eligible patients from study 201 were recruited (webappendix). Patients in study 251 who had previously received bapineuzumab in study 201 were assigned to receive the same dose of bapineuzumab (n=80). Each dose cohort in study 201 had both actively treated and placebo treated patients; in the open-label study the patients who had previously received placebo received the dose of bapineuzumab associated with the dose cohort to which they were originally assigned in study 201 (n=79). No participants from study 202 were enrolled in study 251. MRI scans were done before the first infusion of study drug or placebo and 6 weeks after each subsequent infusion in all studies.

The bapineuzumab phase 2 trials were approved by the local institutional review board at each site, and written informed consent was obtained from each patient (or legally authorised representative). All patients provided consent at entry into the phase 2 studies for the sponsor to access their study data and to do analyses based on these data.

Patients were classified as having incident ARIA-E if they developed new parenchymal or sulcal hyperintensities on FLAIR MRI, consistent with extravascular fluid, in the absence of other pathologies. Parenchymal hyperintensities were recorded as present or absent in the posterior fossa and in the left and right side in each of five regions (frontal, temporal, parietal, occipital, and basal ganglia); we also assessed the overall presence or

Figure 1: Flow chart of patients included in risk analyses
The shaded boxes show the patients who were treated with bapineuzumab and whose MRI scans were reviewed in this study. *ARIA-E were detected in one patient receiving placebo. †ARIA-E were detected in one patient who had metastatic lung cancer, and was not included in the risk factor analyses; the patient was censored at the time of ARIA-E detection. ARIA-E=amyloid-related imaging abnormalities thought to comprise parenchymal vasogenic oedema and sulcal effusions.
absence of sulcal hyperintensities. The total number of regions with ARIA-E was calculated. ARIA-H were also noted as present or absent in the same regions in the T2* images. White matter hyperintensities were classified into four categories, according to an adapted four point scale: 0 (none), 1 (focal lesions), 2 (beginning of confluent lesions), and 3 (diffuse involvement). For the risk analyses, the white matter hyperintensities classified in categories 0 and 1 were combined, as were those in categories 2 and 3, to test whether high-grade white matter hyperintensity (ie, more severe vascular pathology) was associated with ARIA-E.

The risk analyses included data from patients with Alzheimer’s disease treated with bapineuzumab in studies 201, 202, or 251 who had a post-infusion FLAIR MRI scan and no other diagnosed conditions deemed to be responsible for the imaging abnormalities. We focused on the risk factor analyses for ARIA-E; risk analyses for ARIA-H independent of ARIA-E are underway and we plan to report the findings separately. Bapineuzumab dose was defined as the highest dose received. Patients with ARIA-E were classified on the basis of whether ARIA was first identified during studies 201, 202, or 251, or during our MRI review, and as either symptomatic or asymptomatic. A patient was considered symptomatic if one or more symptoms were reported as related or possibly related to study drug in the ARIA safety report by the study investigator.

Statistical analysis
We used Kaplan-Meier analysis to examine the distribution of incident ARIA-E from start of treatment in the different groups and Cox proportional hazards models to analyse risk factors. We used SAS (version 9.1) for all statistical analyses. We assessed the proportional hazards assumption by examining log versus negative log plots; no violations occurred. p value significance thresholds were neither pre-specified nor adjusted for multiplicity.

Role of the funding source
Employees of both sponsors (Janssen Alzheimer Immunotherapy Research and Development, and Pfizer) were involved in the study design, data collection, data analysis, and data interpretation, and the writing and submission of the report. All authors had full access to the study data and shared responsibility for submitting the manuscript for publication.

Results
We reviewed 2572 MRI scans from 262 participants in studies 201, 202, or 251. Of these patients, 223 were ultimately treated with bapineuzumab and 39 were treated with placebo only (figure 1). Two patients (0.8% of all study participants) had ARIA-E that was present on screening MRI, both of whom were subsequently treated with bapineuzumab and excluded from our analysis. An additional ARIA-E case was detected in the central review of the 118 patients treated with placebo.

11 patients treated with bapineuzumab were excluded from our study because they did not have a post-infusion FLAIR MRI. Thus, 210 participants were included in the analysis of risk factors associated with bapineuzumab treatment. One patient identified during our MRI review as possibly having ARIA-E had been diagnosed by the local site investigator during the study as having brain metastases due to lung cancer, and hence considered to have imaging abnormalities not associated with bapineuzumab.

The inter-reader κ was 0.76, with 94% agreement between neuroradiologists about the presence or absence of ARIA-E within individual patients. ARIA-E were observed in 36 of 210 (17%) patients treated with bapineuzumab. Figure 2 shows the range of ARIA
detected in this study. ARIA-E manifested as an increased signal on FLAIR MRI sequences in the white or grey matter parenchyma or within sulcal spaces, whereas ARIA-H were detected on T2*-weighted gradient echo sequences. The baseline prevalence of microhaemorrhage or haemosiderosis (ARIA-H) was 9·2% (19 of 207 participants; table 1). Incident ARIA-H was observed in 17 of 36 (47·2%) of the ARIA-E cases, and in seven of 177 (4·0%) patients without ARIA-E. Of the 17 patients with ARIA-E and incident ARIA-H, 14 had ARIA-H noted on the scan immediately before (n=2), coincident with (n=6), or immediately after (n=6) the scan in which ARIA-E was first noted. Eight of these 14 patients had ARIA-H in the same region as ARIA-E.

Table 1 presents findings from the risk factor analysis. Baseline characteristics were much the same for patients with and without ARIA-E. The incidence of ARIA-E increased with bapineuzumab dose and frequency of APOE ε4 alleles. Table 2 shows proportional hazards models predictive of ARIA-E. The hazard ratios exceeded 3·0 for the two highest doses of bapineuzumab, when compared with the lowest dose. The hazard ratios were about three-times higher in APOE ε4 heterozygous carriers and seven-times higher in APOE ε4 homozygous carriers than in APOE ε4 non-carriers. The hazard ratio did not increase significantly for those patients with small haemosiderin deposits or white matter hyperintensities on baseline MRI scans. When age, sex, baseline mini-mental state examination score, Hamilton depression rating scale score, Rosen-modified Hachinski score, history of cerebrovascular disease, and hypertension were included in the analysis, they were not predictive of ARIA-E.

Figure 3 shows the findings from the Kaplan-Meier analysis by dose, APOE ε4 allele frequency, and the presence of small haemosiderin deposits at baseline. A dose-related increase in ARIA-E risk occurred for the
2 mg/kg dose (figure 3A), particularly after the first infusion. For carriers of APOE ε4 alleles (figure 3B), the analysis showed a clear early difference in risk of ARIA-E that persisted with continued follow-up.

The mean number of infusions before detection of ARIA-E was 2·4 (SD 1·7; range 1–7). Most ARIA-E cases (25 of 36; 69%) were identified after the first or second infusion. ARIA-E was not observed more than 2 years after the first exposure to bapineuzumab. The median duration of ARIA-E for the 31 of 36 patients whose ARIA-E were resolved on follow-up scans was 113 days (IQR 61–182).

Eight patients with ARIA-E identified during the trial received a lower dose after ARIA-E resolved; ARIA-E recurred in one patient, who remained asymptomatic.

Eight of the 36 patients with ARIA-E had adverse events that were considered by the site investigator as related or possibly related to the study drug. The categories for these events were general (n=7, with headache in four), neurological (n=16, with confusion in five), psychiatric (n=3), and gastrointestinal (n=3; webappendix). Of the eight symptomatic patients, seven were APOE ε4 carriers (five homozygous and two heterozygous). Six of the eight symptomatic patients had received a 2 mg/kg dose (n=4) or 1 mg/kg dose (n=2). In all eight cases bapineuzumab was discontinued, and a follow-up MRI scan showed resolution of ARIA-E. One symptomatic patient in study 251 developed a left frontal stroke temporally associated with ARIA-E, but did not have focal symptoms clearly related to the location of either the stroke or the ARIA-E. Although the ARIA-E resolved, the patient eventually died about 8 weeks later because of complications related to the stroke. Seven patients had ARIA-H without ARIA-E; none of these cases manifested clinical symptoms.

15 patients were identified as having ARIA-E only during the MRI re-read. All were asymptomatic and had fewer brain regions involved (mean 1·3, SD 0·5) than patients that persisted with continued follow-up. All of these patients remained asymptomatic. In two of these 13 patients, ARIA-E recurred with additional infusions, but the patients were still asymptomatic.

CSF was collected from eight of 36 patients with ARIA. Five had a normal CSF profile and three had high protein concentrations (259, 264, and 337 mg/dL) and red cell counts (360, 1280, and 108 cells per mm³). Two patients had increased white cell concentrations (8 and 19 cells per mm³). Two patients had increased white cell concentrations (259, 264, and 337 mg/dL) and red cell counts (360, 1280, and 108 cells per mm³), both of whom were symptomatic and APOE ε4 carriers.

Figure 4 shows scans from a patient treated with bapineuzumab (2 mg/kg dose) who developed ARIA in study 202. This patient had ¹¹C Pittsburgh compound B (¹¹C PiB) PET amyloid imaging before and after ARIA. Baseline retention of ¹¹C PiB was increased (consistent with high fibrillar amyloid β burden) in several regions in which ARIA-E and ARIA-H subsequently developed. Retention of ¹¹C PiB was reduced in these regions at the follow-up scan after ARIA-E had resolved.

Discussion
In this retrospective assessment of the incidence of ARIA in bapineuzumab-treated patients from two
A Normal

B Alzheimer’s disease pathology

C Early immunisation

D Repeated immunisation

Figure 5: Model of ARIA mechanisms related to vascular amyloid clearance with anti-Aβ therapy

In the normal physiological state (A), Aβ is thought to be cleared from the brain partly via perivascular and vascular clearance. As Alzheimer’s disease progresses (B), cerebral vessels accumulate vascular amyloid deposition, resulting in disrupted vascular integrity, and impaired perivascular Aβ clearance pathways. Advancing age and APOE ε4 genotype are thought to contribute to the process of increasing cerebral amyloid angiopathy. After initiation of immunotherapy against Aβ (C), targeting removal of Aβ from both parenchyma and the cerebral vasculature, vessels with pre-existing amyloid vascular pathology might become transiently more susceptible to vascular extravasation events, resulting in ARIA-E if the leakage products are proteinaceous fluid and ARIA-H if blood products leak through damaged vessel walls. The degree of increased vascular permeability might depend on the severity of pre-existing cerebral amyloid angiopathy, the efficiency of amyloid clearance, local inflammatory response, and other factors. Mobilisation of parenchymal Aβ with anti-Aβ immunotherapy towards already impaired perivascular drainage pathways could also cause increased fluid accumulation and a paradoxical transient increase in amyloid angiopathy. With repeated immunisation (D) and continued clearance of vascular Aβ, the structural integrity of the vessels and the efficiency of the perivascular clearance pathway should improve, and the risk of such extravasation events should decrease. Portions adapted from Weller and colleagues,9 by permission of John Wiley and Sons. Aβ—amyloid β.

Figure 4: MRI and ¹¹C PiB PET scans of an APOE ε4 heterozygote given bapineuzumab (2.0 mg/kg)

This patient was one of two who had ARIA-E in the 202 study. This patient had ¹¹C PiB PET imaging soon after the onset of the ARIA. Baseline FLAIR image without evidence of ARIA-E (A). FLAIR sequence obtained at week 6 (C) shows bifrontal parenchymal hyperintensity (arrows, ARIA-E) which resolved by week 19 (D). Additionally, week 19 gradient echo T2*−weighted sequence (F) shows the development of bifrontal microhaemorrhages (ARIA-H; arrows) not present on previous images (not shown). A corresponding week 19 ¹¹C PiB scan (E) shows reduced ¹¹C PiB uptake (arrows) compared with that at baseline in regions with ARIA-E and ARIA-H (arrows, B). FLAIR=fluid attenuation inversion recovery. ¹¹C PiB=¹¹C Pittsburgh compound B. ARIA-E=amyloid-related imaging abnormalities thought to be parenchymal vasogenic oedema and sulcal effusions. ARIA-H=amyloid-related imaging abnormalities thought to be a result of microhaemorrhages and haemosiderosis.

phase 2 studies and an open-label study, ARIA was detected in 36 of 210 (17%) patients treated with bapineuzumab. Most cases were clinically silent. Roughly 40% of ARIA cases were first detected in this retrospective review, all of whom were asymptomatic and continued to be treated while having ARIA-E. In some patients, ARIA recurred, but they remained asymptomatic. These newly identified ARIA-E cases appeared to have milder FLAIR signal changes and fewer involved brain regions than did originally identified ARIA-E cases. When the phase 2 studies started, little was known about the range of ARIA changes on MRI. With greater awareness of these abnormalities, it seems likely that local radiologists will miss fewer ARIA cases in the future.

The mechanisms that cause ARIA need to be fully elucidated, but the risk factors identified in this study, as well as data from animal models, suggest potential hypotheses (figure 5). The risk analyses provide quantitative evidence for increased risk of ARIA-E with increasing APOE ε4 allele frequency, which supports a preliminary report suggesting that the risk of ARIA-E is increased in APOE ε4 carriers.1 APOE ε4 has been linked to development of cerebral amyloid angiopathy in transgenic...
mice. Post-mortem studies in people indicate that APOE ε4 is a risk factor for cerebral amyloid angiopathy and spontaneous ARIA-E-like abnormalities have been reported in patients with cerebral amyloid angiopathy. APOE ε4 carrier status is also a risk factor for microhaemorrhage in the general population and in patients in memory clinics. Too few ARIA-E cases occurred to fully test an interaction between APOE ε4 allele frequency and bapineuzumab dose, although that seven of eight symptomatic cases were APOE ε4 carriers and six of eight were treated with the two highest doses is suggestive of a potential relation that should be fully explored in larger studies. Together with the risk factor analyses, these findings suggest that it might be possible to reduce bapineuzumab-related ARIA-E and associated symptoms by careful dosing, with attention to APOE ε4 status.

The presence of baseline ARIA-H was not found to be a significant risk factor for ARIA-E in our study. However, patients with baseline microhaemorrhages were excluded from participation in study 251 because of concern that baseline microhaemorrhages could represent greater cerebral amyloid angiopathy and ARIA-E. About half of the patients treated with bapineuzumab who developed ARIA-E also developed ARIA-H, with most of these patients having evidence of temporal and spatial co-occurrence. These findings suggest that ARIA-E and ARIA-H are related, perhaps both linked to increases in vascular permeability. Dependent on the location (intraparenchymal or meningeal) of the vessel, the leakage of proteinaceous fluid could cause an increased signal in FLAIR images (ARIA-E) in the brain parenchyma (vasogenic oedema) and leptomeningeal spaces (sulcal effusions), whereas leakage of red cells would result in ARIA-H, seen on T2*-weighted gradient echo MRI as effusions), whereas leakage of red cells would result in vasogenic oedema and microhaemorrhage. A report in a small number of patients treated with another monoclonal antibody suggests a possible relation of ARIA-E with vascular amyloid burden. The increased risk of ARIA with a high bapineuzumab dose, the findings from a case with PET amyloid imaging, and a report in a small number of patients treated with another monoclonal antibody suggest a possible relation of ARIA-E with amyloid β clearance. Our findings have important implications for elucidation of the mechanisms underlying ARIA and warrant the close monitoring of ARIA in the development of anti-amyloid therapies for Alzheimer’s disease.

However, similar to transgenic animals, eventual normalisation of cerebral blood vessel integrity in people might also be possible (figure 5D). In post-mortem studies of patients included in an earlier active amyloid immunisation trial (AN1792), two participants had an almost complete absence of cerebral amyloid angiopathy, and they were among those who were followed up for the longest period (approximately 5 years). The finding that most ARIA-E occurred within the first few doses could also support the hypothesis that vascular remodelling after amyloid clearance might reduce the risk of ARIA over time.

ARIA-E seems to rarely occur spontaneously; one case was identified in the placebo group of study 201 and two cases were noted at screening. A report noted two spontaneous ARIA-E cases in more than 3000 patients screened for Alzheimer’s disease clinical trials of semagacestat and solanezumab. In view of reports of similar ARIA findings in patients with cerebral amyloid angiopathy, it is possible that some of these spontaneous ARIA-E cases are patients with Alzheimer’s disease who also have cerebral amyloid angiopathy.

Several potential limitations to our study should be noted. The MRI review was retrospective, and the results might have been different if scans had been read prospectively, without access to other scans for
comparison. The main aim of having two neuro-radiologists to assess the scans was to increase the likelihood of detection of any potential MRI findings consistent with ARIA; therefore, we did not provide extensive training to enhance inter-reader reliability. Nevertheless, the inter-reader reliability was high. Because we asked the readers to then discuss any cases with discrepant reads, we were not able to assess intra-rater reliability. A more detailed rating scale for both ARIA-E and ARIA-H is being developed, and will be used in future studies with the phase 3 data. We did not find evidence of associated clinical symptoms in most ARIA cases, but subtle symptoms could have been missed in patients with mild to moderate dementia. Although this study includes the largest collection of ARIA cases related to treatment to date (panel), because of the small numbers of participants, we cannot definitively explore all potential risk factors, which will require further study in larger trials.

Our results suggest that ARIA consists of a spectrum of imaging findings with variable clinical correlates during the trials, including a substantial number of cases that went undetected and were asymptomatic despite continued treatment. The frequent co-occurrence of ARIA-E and ARIA-H suggests that they share a common pathophysiological mechanism, which might be related to transient increases in vascular permeability. The increased risk of ARIA in APOE ε4 carriers further supports a key role for vascular amyloid, whereas the relation with bapineuzumab dose and the 11C PiB PET amyloid findings suggest that ARIA could be related to amyloid clearance. Ongoing studies with bapineuzumab and other potential amyloid-modifying therapies should provide further insight into the long-term implications of these abnormalities.

Contributors
RS contributed to the study conception and design, data analysis and interpretation, literature searches, writing of the introduction and discussion sections, critical revision of the Article, and figure preparation. SS contributed to the study design, data analysis and interpretation, and writing of the Article. DJB contributed to planning and to reviewing and editing the Article. DT contributed to the study design, and reviewed the MRI images and the Article. IB contributed to the study design, implementation, review of the Article, and review of the Article. MR contributed to the study design, implementation, data collection, data interpretation, and writing. APP participated in the study design, data collection, data interpretation, and writing. IL was involved with the study design, collection, analysis, and interpretation of data, and the development of the Article. HMA contributed to the study design and implementation, the analysis and interpretation of data, and the development of the Article. KAM contributed to writing and reviewing the Article. YL contributed to the study design, study implementation, and data analysis. EL contributed to the study design, implementation, review of analyses, and Article writing and review. RMG provided statistical input and review. HRB was involved in the study design, data collection, interpretation and analysis, and development and submission of the Article. GGK contributed to writing, figure preparation, literature review, and Article preparation. RB contributed to the study design, analysis, interpretation of data, and review of the Article. MG contributed to the study design, study conduct, data analysis, and writing.

Conflicts of interest
RS has served as a study investigator and a consultant for Janssen Alzheimer Immunotherapy Research and Development, and for Pfizer, and has received honoraria for participation in symposia. She has also served as a consultant or site investigator or both for Bristol-Myers Squibb, Roche, Elan, Biogen-IDEC, Avid, and Bayer. SS has served as a consultant and study investigator for Janssen Alzheimer Immunotherapy Research and Development, Pfizer, and Elan Corporation phase 2 and 3 studies of bapineuzumab. DT provides review of MRI images for Janssen Alzheimer Immunotherapy Research and Development. JB serves as a neuroradiological consultant to SYNARC, an imaging contract research organisation contracted by both sponsors companies; he also serves as a consultant to Janssen Alzheimer Immunotherapy Research and Development for non-clinical research activities. NCF has provided consulting or image analysis services or both to Elan Corporation, Janssen Alzheimer Immunotherapy Research and Development, Pfizer, Wyeth Pharmaceuticals, AstraZeneca, Bristol-Myers Squibb, Eli Lilly and Company, GE Healthcare, Lundbeck A/S, and IXICO. MR serves as consultant to Janssen Alzheimer Immunotherapy Research and Development. MS participates in a consulting and advisory capacity for Eli Lilly and Company, Amerisciences, Takeda Pharmaceuticals, Eisai, Pfizer, and GlaxoSmithKline, and receives royalties from Wiley and AmeriSciences. He receives contracting fees and grants from Celgene Corporation, Genentech, and Eisai. LSH serves on the study steering committee and has acted as a consultant for Janssen Alzheimer Immunotherapy Research and Development, but receives less than US$10000 yearly for such consulting activities. APP has received grant and research support from Baxter International, Bristol-Myers Squibb, Eisai, Elan Corporation, Genentech, Hoffmann-La Roche, Janssen Alzheimer Immunotherapy Research and Development, Medivation, Pfizer, and Toyama Chemical Co. He has also served as a consultant and participated on advisory boards for Elan Corporation. Janssen Alzheimer Immunotherapy Research and Development, Medivation, Pfizer, Transition Therapeutics, and Toyama Chemical Co. He is also a member of the speakers’ bureau for Forest Laboratories. RB is an employee of and receives stock and stock options from Pfizer. HMA, KAM, YL, EL, KMG, HRB, and GGK are employees of Janssen Alzheimer Immunotherapy Research and Development. LSH, HMA, KAM, YL, EL, KMG, and GGK are stockholders in Elan Corporation. MG is a consultant to Janssen Alzheimer Immunotherapy Research and Development and is a stockholder in Elan Corporation. DJB declares no conflicts of interest.

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