Effect of Immunotherapy With Bapineuzumab on Cerebrospinal Fluid Biomarker Levels in Patients With Mild to Moderate Alzheimer Disease

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Background: Given the slow and variable clinical course of Alzheimer disease, very large and extended clinical trials are needed to identify a beneficial clinical effect of disease-modifying treatments. Therefore, biomarkers are essential to prove that an anti–β-amyloid (Aβ) drug candidate affects both Aβ metabolism and plaque load as well as downstream pathogenic mechanisms.

Objective: To evaluate the effect of the anti–Aβ monoclonal antibody bapineuzumab on cerebrospinal fluid (CSF) biomarkers reflecting Aβ homeostasis, neuronal degeneration, and tau-related pathology in patients with Alzheimer disease.

Design: Two phase 2, multicenter, randomized, double-blind, placebo-controlled clinical trials of 12-month duration.

Setting: Academic centers in the United States (Study 201) and England and Finland (Study 202).

Patients: Forty-six patients with mild to moderate Alzheimer disease.

Interventions: Patients received either placebo (n = 19) or bapineuzumab (n = 27) in 3 or 4 ascending dose groups.

Main Outcome Measures: Changes between end of study and baseline in the exploratory CSF biomarkers Aβ1-42, AβX-42, AβX-40; total tau (T-tau); and phosphorylated tau (P-tau).

Results: Within the bapineuzumab group, a decrease at end of study compared with baseline was found both for CSF T-tau (−72.3 pg/mL) and P-tau (−9.9 pg/mL). When comparing the treatment and placebo groups, this difference was statistically significant for P-tau (P = .03), while a similar trend for a decrease was found for T-tau (P = .09). No clear-cut differences were observed for CSF Aβ.

Conclusions: To our knowledge, this study is the first to show that passive Aβ immunotherapy with bapineuzumab results in decreases in CSF T-tau and P-tau, which may indicate downstream effects on the degenerative process. Cerebrospinal fluid biomarkers may be useful to monitor the effects of novel disease-modifying anti–Aβ drugs in clinical trials.

Trial Registrations: clinicaltrials.gov Identifier: NCT00112073, EudraCT Identifier: 2004-004120-12, and isrctn.org Identifier: ISRCTN17517446.

humanized anti-Aβ antibodies or intravenous immunoglobulins. The intended effect is thought to be mediated by anti-Aβ antibodies that either bind to Aβ plaques or other forms of Aβ aggregates in the brain, thereby inducing Aβ clearance by microglia or by binding soluble Aβ in the periphery, thereby driving an efflux of Aβ from the brain. Preclinical studies in transgenic mice producing excess Aβ have shown that antibodies directed against the N-terminus of Aβ enter the brain and reduce amyloid deposits in both brain tissue and the cerebral vasculature. These antibodies also block the synaptic toxic effects of Aβ oligomers and improve performance in amyloid precursor protein transgenic mice. Previous Aβ immunotherapy trials in humans using active immunization with the full-length Aβ42 peptide suggested clinical benefits.

Bapineuzumab, an antibody targeted against the N-terminus of Aβ, was previously evaluated in phase 2 multicenter trials on passive Aβ immunotherapy in AD, and is currently being evaluated in phase 3 trials. In this exploratory post hoc pooled analysis, we evaluated whether bapineuzumab impacted the CSF levels of the downstream biomarkers, total tau (T-tau) and phosphorylated tau (P-tau), and the primary biomarker Aβ in these completed trials.

### METHODS

Two phase 2, multicenter, randomized, double-blind, placebo-controlled, multiple-ascending dose studies were conducted at 30 sites in the United States (Study 201) and 3 clinical sites in Europe (2 in England and 1 in Finland) (Study 202). Study 201 enrolled 234 patients, randomly assigned to either placebo or intravenous bapineuzumab in 4 dose cohorts (0.15, 0.5, 1.0, or 2.0 mg/kg). Study 202 enrolled 28 patients randomized to either placebo or intravenous bapineuzumab in 3 ascending dose cohorts (0.5, 1.0, or 2.0 mg/kg). Patients received 6 infusions, 13 weeks apart, with final assessments at week 78 (Table 1).

Both studies included a substudy in which CSF was collected when clinicians agreed to perform and patients consented to undergo lumbar puncture. Cerebrospinal fluid was taken before treatment initiation and at week 54 (approximately 2 weeks after the week 52 study drug infusion). Study 201 enrolled 35 substudy patients (20 taking bapineuzumab and 15 taking placebo) and Study 202 enrolled 11 CSF substudy patients (7 taking bapineuzumab and 4 taking placebo), with paired baseline and post-baseline samples (Figure 1). Patient demographics are presented in Table 2.

Each patient underwent clinical assessments of cognition and function, volumetric and safety magnetic resonance images (MRIs), and safety evaluations. Subjects in Study 202 also underwent carbon 11-labeled Pittsburgh Compound B positron emission tomography and [18F]-fluorodeoxyglucose positron emission tomographic imaging. An independent safety monitoring committee assessed the safety of treatment throughout the trial. Eligible patients met the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association criteria for probable AD, had an MRI consistent with AD, and a score of 4 or less on the Rosen-modified Hachinski Ischemic Score.

Study 201 enrolled subjects who had a score of 16 to 26 on the Mini-Mental State Examination scale, while Study 202 enrolled subjects with a score of 18 to 26. Patients were excluded if they had clinically significant neurologic or psychiatric disease other than AD, while treatment with cholinesterase inhibitors or memantine at a stable dose for at least 120 days before screening was allowed. One placebo subject had a CSF T-tau level of 2490 pg/mL at screening and a reduction of 1541 pg/mL at week 54. It was reported that this subject fell within the first week of the study, and he may have fallen previously. A fall due to a minor stroke or with concussion might explain the high CSF T-tau at baseline and its subsequent drop; declines in CSF T-tau of 1500 pg/mL are not normal for patients with AD without some other explanation. Therefore, all data points from this subject were excluded from the analysis.

Study 201 (clinicaltrials.gov Identifier: NCT00112073) was approved by each site’s local institutional review board, while Study 202 (EudraCT Identifier: 2004-004120-12 and isrctn.org Identifier: ISRCTN17517446) was approved by each site’s local independent ethics board. For both studies, written informed consent was obtained from each patient (or legally authorized representative).

### LUMBAR PUNCTURE AND CSF ASSAYS

Cerebrospinal fluid samples were obtained by lumbar puncture. Cerebrospinal fluid was collected in polypropylene tubes to avoid absorbance of proteins to the test-tube walls. All CSF samples were gently mixed to avoid possible gradient effects, centrifuged, aliquoted, frozen, and stored at −80°C, pending biochemical analyses. A corresponding blood sample was obtained at the time of the lumbar puncture.
Cerebrospinal fluid T-tau was analyzed using a sandwich enzyme-linked immunosorbent assay (ELISA) (Innotest hTAU-Ag; Innogenetics), which measures all tau isoforms irrespective of phosphorylation status. Phosphorylated tau in CSF was analyzed using a sandwich ELISA method (Innotest Phospho-tau [181P]; Innogenetics). Cerebrospinal fluid Aβ1-42 was measured using a sandwich ELISA (Innotest β-amyloid (1-42); Innogenetics), as previously described. In this assay, the monoclonal antibody 3D6, which is specific to the N-terminus (epitope Aβ1-5), was used as a detector. Cerebrospinal fluid AβX-42 was analyzed using a modified sandwich ELISA in which the 4G8 monoclonal antibody, which has the epitope Aβ18-22, was used as detector antibody, thus it measures all N-terminally truncated AβX3 species. The AβX-40 in CSF was analyzed using the MS6000 Human Ultra-Sensitive Aβ40 Kit (Meso-Scale Discovery). All CSF analyses were performed at the end of study at the Clinical Neurochemistry Laboratory, Sahlgrenska University Hospital, Mölndal, Sweden, by certified laboratory technicians. All CSF samples were analyzed in 1 batch, with paired samples from individual patients side by side on the same plate. Serum bapineuzumab concentrations were measured by a validated sandwich ELISA method with a range of quantification from 1.98 to 147 ng/mL, while the bapineuzumab concentration in human CSF was measured by a validated electrochemiluminescence method with a range of quantification from 1.56 to 200 ng/mL.

STATISTICAL ANALYSIS

The analysis compared the bapineuzumab group with the placebo group using an analysis of covariance model. The primary outcome was the change between end of study (week 54) and baseline CSF biomarker levels. The explanatory variables were treatment group (bapineuzumab vs placebo) and screening value of the outcome of interest as a continuous covariate. The analysis was a 2-sided test of the week 54 least squares mean values were not imputed). Given the small sample size of each cohort and lack of a clear efficacy dose response, all dose levels of bapineuzumab (or placebo) were pooled in the analysis. In addition, the data from the 2 studies were combined and analyzed using the same analysis of covariance model as for the individual study, except that study was included as an additional exploratory variable to adjust for differences between Study 201 and Study 202. All analyses were performed with SAS version 9.1 (SAS Institute).

Neither Study 201 nor Study 202 were designed or powered as an efficacy study. The sample size for each study was calculated to ensure 80% or greater probability of detecting an adverse event that occurred with a rate of at least 5% within a single bapineuzumab-treated dose cohort. The CSF substudy was optional to participants who consented to the additional procedures, thus the sample size for the substudy was not a priori specified. The analyses were considered exploratory and P values were not adjusted for multiplicity. Statistical differences were noted if the calculated P < .05.

The combined analysis of Study 201 and Study 202 included a total of 27 bapineuzumab-treated and 19 placebo-treated subjects with paired baseline and end of study samples, most of whom had all 6 intended doses of bapineuzumab (Table 1). No significant differences were found in basic demographic variables between the bapineuzumab and placebo groups or between subjects that completed the CSF substudy and the drop-outs (Table 2). Some minor differences in age, height, and duration of disease were found between the subjects in the CSF substudy and those who did not enroll (Table 2), but we found no evidence in the literature that such factors would influence the longitudinal change in CSF biomarker levels during a 1-year period.
CSF T-tau

In pooled analysis from Study 201 and Study 202 (Table 3, Figure 2), a decrease in CSF T-tau was observed at end of study compared with baseline in the bapineuzumab-treated group (−72.3 pg/mL, P = .03), while there was no difference in the placebo group (−5.6 pg/mL, P = .80). When comparing the change from baseline to end of study, a trend for a decrease in CSF T-tau at end of study was found in bapineuzumab cases compared with placebo cases (−66.7 pg/mL, P = .09).

CSF P-tau

In pooled analysis of Study 201 and Study 202 (Table 3, Figure 2), a decrease in CSF P-tau was observed at end of study compared with baseline in the bapineuzumab-treated group (−9.9 pg/mL, P = .001), while there was no difference in CSF P-tau levels in the placebo group. When comparing the change from baseline to end of study between the bapineuzumab-treated cases with placebo subjects, a treatment decrease was observed (−7.3 pg/mL, P = .03).

CSF Aβ

In the pooled analysis of Study 201 and Study 202, there were no notable differences in CSF Aβ42-4 or AβX-40 at end of study (week 54) compared with baseline within the bapineuzumab group, or when comparing the change between end of study and baseline between the bapineuzumab and placebo groups (Table 3, Figure 2). There was a modest increase in CSF AβX-42 (Table 3, Figure 2) at end of the study compared with baseline within the bapineuzumab-treated group (−9.9 pg/mL, P = .001), while there was no difference in CSF P-tau levels in the placebo group. When comparing the change from baseline to end of study between the bapineuzumab-treated cases with placebo subjects, a treatment decrease was observed (−7.3 pg/mL, P = .03).

Table 2. Patient Demographics

<table>
<thead>
<tr>
<th>Group</th>
<th>CSF Study in Pooled Trials 201 and 202</th>
<th>Completers vs Drop-Outs in CSF Substudy</th>
<th>Enrolled and Completed CSF Substudy vs Not Enrolled</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Bapineuzumab</td>
<td>Placebo</td>
<td>P Value</td>
</tr>
<tr>
<td>Total, No.</td>
<td>27</td>
<td>19</td>
<td>.50</td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
<td>66.5 (8.9)</td>
<td>64.8 (7.8)</td>
<td></td>
</tr>
<tr>
<td>Female, No. (%)</td>
<td>11 (40.7)</td>
<td>10 (52.6)</td>
<td>.43</td>
</tr>
<tr>
<td>White, No. (%)</td>
<td>26 (96.3)</td>
<td>19 (100.0)</td>
<td>.&gt;99</td>
</tr>
<tr>
<td>Weight, mean (SD), kg</td>
<td>75.9 (15.4)</td>
<td>75.9 (13.2)</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>Height, mean (SD), cm</td>
<td>170.6 (9.2)</td>
<td>168.6 (10.0)</td>
<td>.49</td>
</tr>
<tr>
<td>APOE ε4 carrier, No. (%)</td>
<td>16 (59.3)</td>
<td>11 (57.9)</td>
<td>.93</td>
</tr>
<tr>
<td>Duration, mean (SD), y</td>
<td>4.0 (1.6)</td>
<td>4.9 (3.3)</td>
<td>.27</td>
</tr>
<tr>
<td>MMSE, mean (SD)</td>
<td>20.7 (2.8)</td>
<td>20.5 (3.6)</td>
<td>.84</td>
</tr>
<tr>
<td>MMSE stratum low, 16-21, No. (%)</td>
<td>17 (63.0)</td>
<td>12 (63.2)</td>
<td>.99</td>
</tr>
<tr>
<td>ChE-I or memantine treatment, No. (%)</td>
<td>27 (100.0)</td>
<td>19 (100.0)</td>
<td>NA</td>
</tr>
<tr>
<td>Married, No. (%)</td>
<td>25 (92.6)</td>
<td>16 (84.2)</td>
<td>.78</td>
</tr>
<tr>
<td>Education, mean (SD), y</td>
<td>13.7 (2.8)</td>
<td>14.6 (3.1)</td>
<td>.28</td>
</tr>
<tr>
<td>First degree relatives with AD, No. (%)</td>
<td>12 (44.4)</td>
<td>9 (47.4)</td>
<td>.84</td>
</tr>
</tbody>
</table>

Abbreviations: AD, Alzheimer disease; APOE, apolipoprotein E; ChE-I, cholinesterase inhibitor; CSF, cerebrospinal fluid; MMSE, Mini-Mental State Examination.

a P values were from 2 sample t tests for continuous variables and χ² or Fisher exact tests for categorical variables.
In this study, 1 patient in the bapineuzumab group had MRI evidence of amyloid-related imaging abnormalities–edema/effusion (ARIA-E) for this treatment duration will be needed to identify clinical effects of disease-modifying drugs. For this reason, theragnostic markers may be valuable to identify and monitor the biochemical effect of a novel drug.20 Biomarker evidence that the drug affects both the primary target and downstream pathogenic mechanisms will also be essential to label the drug as being disease modifying.20 In this study, 1 patient in the bapineuzumab group had MRI evidence of amyloid-related imaging abnormalities–edema/effusion (ARIA-E) for this patient. Cerebrospinal fluid safety biomarkers showed a normal CSF to serum albumin ratio (5.4 at baseline vs 5.0 at time of ARIA-E; reference value <10.2) and IgG index (0.41 at baseline vs 0.51 at time of ARIA-E; reference value <0.63), as well as no oligoclonal IgG bands in CSF, either at baseline or at the time of ARIA-E. The pharmacokinetic characteristics of bapineuzumab include a small distribution volume, slow clearance, and long terminal half-life. The ratio of bapineuzumab concentrations increased with dose. Thus, the average ratios of CSF to serum bapineuzumab concentrations were consistent at approximately 0.3% (Figure 3). No anti-bapineuzumab antibodies were detected in any subject.

**CSF SAFETY ASSESSMENTS**

Summaries of safety findings have been previously reported.8,10 In this study, 1 patient in the bapineuzumab group had MRI evidence of amyloid-related imaging abnormalities thought to represent vasogenic edema or sulcal effusions.10 Cerebrospinal fluid samples were taken both at baseline and at the time of the amyloid-related imaging abnormalities–edema/effusion (ARIA-E) for this patient. Cerebrospinal fluid safety biomarkers showed a normal CSF to serum albumin ratio (5.4 at baseline vs 5.0 at time of ARIA-E; reference value <10.2) and IgG index (0.41 at baseline vs 0.51 at time of ARIA-E; reference value <0.63), as well as no oligoclonal IgG bands in CSF, either at baseline or at the time of ARIA-E. The CSF AD biomarkers showed typical values for AD, and they were stable between baseline and at the time of ARIA-E (796 vs 720 pg/mL for T-tau, 78 vs 75 pg/mL for P-tau, and 307 vs 240 pg/mL for Aβ1-42).

**COMMENT**

Passive immunotherapy with antibodies against Aβ, such as bapineuzumab,9 is one of the major disease-modifying therapeutic approaches being evaluated for AD. Because the clinical course is slowly progressive and highly variable in AD, very large clinical trials with extended treatment duration will be needed to identify clinical effects of disease-modifying drugs. For this reason, theragnostic markers may be valuable to identify and monitor the biochemical effect of a novel drug.20 Biomarker evidence that the drug affects both the primary target and downstream pathogenic mechanisms will also be essential to label the drug as being disease modifying.20 In this context, biomarkers in anti-Aβ clinical trials can be divided into primary (pharmacodynamic) biomarkers used to monitor the specific biochemical mode of action of the anti-Aβ drug and downstream biomarkers used to monitor effects on downstream pathogenic processes, such as the neuronal degeneration or tangle formation, downstream of the drug target.21

| Table 3. Changes from Baseline to Week 54 in CSF Biomarker Levelsa |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|
| Biomarker | Treatment (No.) | Observed Mean (SD) | Mean Change (95% CI) | P Value |
| CSF total tau | Bapineuzumab (n = 27) | 811.3 (466.3) | −72.3 (−141.9 to −2.7) | .03 |
| | Placebo (n = 19) | 1077.9 (935.1) | −5.6 (−65.3 to 54.1) | .80 |
| | Bapineuzumab vs placebo | −266.6 (697.3) | −66.7 (−161.3 to 27.9) | .09 |
| CSF P-tau | Bapineuzumab (n = 27) | 97.0 (41.3) | −9.9 (−16.2 to −3.6) | .001 |
| | Placebo (n = 19) | 105.3 (49.8) | −2.6 (−9.6 to 4.4) | .88 |
| | Bapineuzumab vs placebo | −8.3 (45.0) | −7.3 (−16.5 to 2.0) | .03 |
| CSF Aβ1-42 | Bapineuzumab (n = 27) | 364.0 (170.0) | −10.5 (−30.7 to 9.8) | .44 |
| | Placebo (n = 19) | 382.8 (151.8) | −6.1 (−40.7 to 28.6) | .75 |
| | Bapineuzumab vs placebo | −18.8 (168.4) | −4.4 (−40.9 to 32.1) | .79 |
| CSF AβX-42 | Bapineuzumab (n = 27) | 499.6 (305.9) | 32.2 (−38.5 to 102.9) | .02 |
| | Placebo (n = 19) | 524.1 (228.7) | 13.8 (−56.1 to 83.8) | .06 |
| | Bapineuzumab vs placebo | −24.4 (276.9) | 18.4 (−81.7 to 118.5) | .89 |
| CSF Aβ1-40 | Bapineuzumab (n = 26) | 6755.9 (2287.5) | −188.5 (−916.9 to 539.9) | .78 |
| | Placebo (n = 19) | 7405.8 (3356.9) | −700.4 (−1612.1 to 211.2) | .09 |
| | Bapineuzumab vs placebo | −649.9 (2765.6) | −76.4 (−831.8 to 678.9) | .84 |

Abbreviations: Aβ, β-amyloid; CSF, cerebrospinal fluid; P-tau, phosphorylated tau.

a Changes from baseline were analyzed using analysis of covariance models with model terms for treatment and baseline value. An additional covariate study was included in the combined analysis of Studies 201 and 202. One subject was not included in the analysis as explained in Methods.
Zumab in CSF to serum was stable between the dose cohorts, with a mean of approximately 0.3%. The CSF to serum ratio for total IgG is also approximately 0.3%, suggesting that bapineuzumab passes the blood-brain barrier at the expected ratio for IgG antibodies.

In our study, we found a decrease in CSF P-tau in the bapineuzumab group, while no change was found in the placebo group. In addition, there was a treatment decrease in CSF P-tau at study end for the bapineuzumab-treated compared with placebo-treated subjects. Phosphorylated tau measured in CSF samples taken during life correlate with neocortical tangle pathology at autopsy, and CSF P-tau also correlates with the rate of hippocampal atrophy in the brain. The CSF level of P-tau thus seems to reflect the phosphorylation state of tau and the formation of tangles in the brain.

Bapineuzumab reduces brain levels of P-tau, which may also reduce the formation of tangles in the brain. In addition, the downstream biomarker CSF T-tau decreased with treatment in the bapineuzumab group, while no change was found in the placebo group. This is consistent with the reduction in CSF T-tau seen in the AN1792 trial with active Aβ immunotherapy. Cerebrospinal fluid T-tau levels correlate with the amount of damaged tissue and poor clinical outcome in acute brain disorders, and high T-tau has also been associated with fast progression from mild cognitive impairment to AD and with rapid cognitive decline and a high mortality rate in patients with AD, suggesting that the CSF level of T-tau reflects the intensity of the neuronal degeneration. The reduction in the downstream biomarker CSF T-tau with bapineuzumab treatment warrants further investigation into the potential for this drug to attenuate the intensity of the neurodegenerative process.

Bapineuzumab is hypothesized to bind to Aβ in the brain, thereby facilitating its clearance. In support of this hypothesis, we previously reported that bapineuzumab treatment results in a modest reduction in cortical binding of the Aβ ligand Pittsburgh Compound B as evaluated by positron emission tomography.
Our study, both a base- 

Electronic image changes referred to as ARIA-E appears to 

levels of T-tau, P-tau, and Aβ; no oligoclonal IgG bands in CSF; and stable CSF 

line CSF sample and a sample at the time of ARIA-E were 

signs of additional neuronal damage. 

One limitation is that this study is based on pooled 

analysis of the bapineuzumab trials Study 201 and Study 

202. This was done to increase the sample size of pa- 

tients in each substudy with paired CSF samples. How- 

ever, for both trials, CSF biomarkers were analyzed in 

the same laboratory using the same assay formats, CSF 

samples from individual cases were analyzed side by side 

on the same ELISA plate, and data were analyzed as the 

change in biomarker levels between baseline and end of 

study. This procedure will minimize variation and al- 

low pooling of CSF data. 

In summary, in a pooled analysis of CSF data from 2 

phase 2 clinical trials on passive immunotherapy with 

bapineuzumab in patients with mild to moderate AD, a 

decrease in both P-tau and T-tau at end of study com- 
pared with baseline within the bapineuzumab group was 

observed. For CSF P-tau, a statistically significant treat- 

ment difference was observed between the bapineu- 

zumab and placebo groups. These findings may indi- 

cate downstream effects of bapineuzumab treatment on 

the degenerative process. An important question re- 
mains whether such changes in CSF biomarkers corre- 

late with clinical benefit.21 This question will be ad- 

dressed in the ongoing bapineuzumab phase 3 trials. 

Figure 3. Pharmacokinetics of bapineuzumab. Cerebrospinal fluid (CSF) to 

serum concentrations of bapineuzumab at different doses at end of study 
(week 54). Values given as mean (standard error of the mean) (percentage). 
Ten cases at a treatment dose of 0.15 mg/kg, 5 cases at 0.5 mg/kg, 6 cases 
at 1.0 mg/kg, and 4 cases at 2.0 mg/kg. The mean (standard error of the 
mean) absolute bapineuzumab levels in serum and CSF were 1850 (118) 
ng/mL and 4.9 (1.2) ng/mL, respectively, in the 0.15 mg/kg cohort; 
6290 (1060) ng/mL and 18.1 (6.0) ng/mL, respectively, in the 0.5 mg/kg 

cohort; 11 460 (1700) ng/mL and 27.2 (5.1) ng/mL, respectively, in the 1.0 

mg/kg cohort; and 17 660 (1510) ng/mL and 44.7 (7.7) ng/mL, respectively, 
in the 2.0 mg/kg cohort.

Cerebrospinal fluid biomarkers may be valuable for 
safety monitoring in AD clinical trials.20 Magnetic reso- 
nance imaging, both as compared with base- 

line and with placebo-treated patients.19 Because the popu- 
lation in this study is not identical to that in the positron 
emission tomography study, the number of cases with both 
investigations is too small to allow any comparisons. In the 
AD brain, a relatively large proportion of Aβ is N- 
terminal truncated or modified.20 For this reason, we ana- 
lyzed Aβ42 by 2 different ELISA methods, 1 for Aβ1-42 to 
measure full-length Aβ42 peptides and 1 for AβX-42, which 
also captures Aβ isoforms that are N-terminally modified. 
We were not able to identify any change in CSF AβX-42 
or in Aβ1-42 or AβX-40 that differed between the bapineu- 
zumab and placebo groups. Similarly, CSF Aβ42 levels were 
also minimally affected in the AN1792 immunotherapy trial.8 
This lack of change in CSF Aβ42 may be attributed to clear- 
ance of cortical Aβ through other pathways than CSF or, 
alternatively, oligomerization of Aβ or binding of Aβ to cha- 
petrone or to the therapeutic antibody that masks a change 
in CSF Aβ with treatment. For these reasons, the Aβ results 
have to be interpreted with caution. 

Cerebrospinal fluid biomarkers may be valuable for 
safety monitoring in AD clinical trials.20 Magnetic resonan- 
ce image changes referred to as ARIA-E appears to 

be a safety concern with bapineuzumab treatment.19 In 
our study, both a baseline CSF sample and a sample at the time of ARIA-E were 
available in the single patient who developed ARIA-E. This 
case had normal and stable CSF levels of both albumin 
and IgG; no oligoclonal IgG bands in CSF; and stable CSF 
levels of T-tau, P-tau, and Aβ42, which were compat- 
ible with the clinical diagnosis of AD. Thus, in this pa- 
tient, ARIA-E was not accompanied by blood-brain bar- 
rier dysfunction, inflammatory reactions, or tau-related 
signs of additional neuronal damage.

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