# SYNOPSIS

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|---|---|
| Name of Sponsor/Company | Janssen Alzheimer Immunotherapy |
| Name of Finished Product | Not available |
| Name of Active Ingredient(s) | Bapineuzumab (AAB-001, ELN115727) |

**Protocol No**.: ELN115727-301

**Title of Study**: A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Efficacy and Safety Trial of Bapineuzumab (AAB 001, ELN115727) in Subjects With Mild to Moderate Alzheimer's Disease who are Apolipoprotein E *E4* Noncarriers

**EudraCT Number**: 2009-012748-17

**NCT No**.: NCT00574132 **Clinical Registry No**.: ELN115727-301

**Coordinating Investigator(s):**

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**Study Center(s)**: The numbers in the parentheses include sites that screened and/or enrolled subjects: Austria (2 sites), Canada (17 sites), Germany (4 sites), and United States (195 sites).

**Publication (Reference):** None

**Study Period**: 21 December 2007 – 05 June 2012 (ie first subject enrolled – last subject last visit). Database Lock: 17 July 2012

**Phase of Development**: 3

**Outcome**: This study did not meet its primary efficacy objectives.

**Hypotheses**: The 2 coprimary efficacy hypotheses were the following:

- Bapineuzumab is superior to placebo as measured by change from baseline to Week 78 in the Alzheimer's Disease Assessment Scale – Cognitive subscale (ADAS-Cog/11) total score
- Bapineuzumab is superior to placebo as measured by change from baseline to Week 78 in the Disability Assessment Scale for Dementia (DAD) total score.

The 3 key biomarker secondary hypotheses are the following:

- Bapineuzumab is superior to placebo as measured by change from baseline to Week 71 in cortical brain amyloid burden as measured by Pittsburgh Compound B (PiB) positron emission tomography (PET) global cortical average (GCA) standardized uptake value ratios (SUVr).
- Change from baseline to Week 71 in cerebrospinal fluid (CSF) phosphorylated tau (p-tau) concentrations.
- Change in brain volume as measured by the Week 71 brain boundary shift integral (BBSI) on volumetric magnetic resonance imaging (vMRI) scans.

**Objectives**:

**Primary Objectives and Endpoints**: To demonstrate the efficacy of multiple doses of intravenously (IV)-administered bapineuzumab (0.5- and 1.0-mg/kg) compared to placebo, in subjects with mild to moderate Alzheimer's disease (AD), by measuring the change from baseline to Week 78 in ADAS-Cog/11 total score and DAD total score.

**Key Clinical Secondary Objectives and Endpoints**: To demonstrate the effect of bapineuzumab IV (0.5- and 1.0-mg/kg) compared to placebo on time to first clinically meaningful deterioration by measuring ADAS-Cog/11 total score time to first clinically meaningful deterioration and DAD total score time to first clinically meaningful deterioration; and to demonstrate the effect of bapineuzumab IV (0.5- and 1.0-mg/kg) compared to placebo on subject dependence (amount of assistance needed) by measuring the change from baseline to Week 78 in the Dependence Scale (DS) total score.

**Key Biomarker Secondary Objectives and Endpoints**: To demonstrate the effect of bapineuzumab IV (0.5- and 1.0-mg/kg) compared to placebo on biomarkers that are indicative of disease pathophysiology in substudies of subjects by measuring the change from baseline to Week 71 in brain amyloid burden, p-tau levels in CSF, and brain volume.

**Key Divergence of Effect Secondary Objective and Endpoints**: To demonstrate divergence of effect (increasing separation with time compared with placebo) observed with bapineuzumab IV (0.5- and 1.0-mg/kg) on ADAS-Cog/11 total score or DAD total score from Week 39 to Week 78.

**Other Secondary Objectives and Endpoints**: To demonstrate the effect of bapineuzumab IV (0.5- and 1.0-mg/kg) compared to placebo in change from baseline to Week 78 in the Clinical Dementia Rating Scale - Sum of Boxes (CDR-SB) total score; and to demonstrate the effect of bapineuzumab IV (0.5- and 1.0-mg/kg) compared to placebo on the proportions of responders by measuring the proportions of subjects with worsening from baseline to Week 78 of <7 points on the ADAS-Cog/11 total score, <12 points on the DAD total score, ADAS-Cog/11 total score cumulative response, or DAD total score cumulative response.

**Safety Objective and Endpoints**: To assess the safety of bapineuzumab IV compared to placebo by measuring the incidence and severity of treatment-emergent adverse events (TEAEs) and clinically important changes in safety assessment results.

**Exploratory Objectives and Endpoints**: To evaluate the effect of bapineuzumab IV on other biomarker, clinical, pharmacokinetic (PK), pharmacodynamic (PD), immunogenicity, health outcomes, and pharmacogenomic measures.

**Methodology**: This was a multicenter, randomized, double-blind, placebo-controlled, parallel–group, out-patient study in subjects with mild to moderate AD who were *APOE*E4* noncarriers. Subjects eligible for the study were randomized to receive bapineuzumab at 1 of 2 dose levels, 0.5-mg/kg or 1.0-mg/kg, or placebo by infusion every 13 weeks. Subjects were randomized using stratified randomization. The strata

included current cholinesterase inhibitor or memantine use (yes versus no), baseline mini-mental state examination (MMSE) total score (low=16 to 21 versus high=22 to 26), and participation in the substudies (eg, PET, CSF, vMRI, and PK/PD/electrocardiogram [ECG]). Safety was monitored by an Independent Safety Monitoring Committee (ISMC).

**Number of Subjects (planned and analyzed)**: The planned total sample size was approximately 1450 subjects. In the original protocol, subjects were randomized to receive bapineuzumab (0.5-, 1.0-, and 2.0-mg/kg) versus placebo in a 1:1:1:2 ratio. The 2.0-mg/kg dose level was discontinued due to the Sponsor's decision on 02 April 2009 (Protocol Amendment 1). Subjects who were randomized to the 2.0-mg/kg dose level continued in the study, and were reassigned to receive bapineuzumab at the 1.0-mg/kg dose level for the remainder of the study. Therefore, approximately 750 subjects were randomized in a 3:3:4 bapineuzumab 0.5-mg/kg:1.0-mg/kg:placebo ratio; and approximately 150 subjects were randomized under the original protocol to the 2.0-mg/kg dose level.

Subjects randomized to the 2.0-mg/kg dose level were not included in the primary or secondary efficacy analyses. This study included a PK/PD/ECG substudy and 3 biomarker substudies as follows: a brain amyloid PET substudy, a CSF substudy, and a volumetric brain MRI substudy. The number of subjects in each analysis population is summarized in Table S-1.

**Table S-1 Number of Subjects in Each Analysis Population by Treatment Group**

| | Placebo | Bapineuzumab | | | |
|---|---|---|---|---|---|
| | | | | Pooled | |
| | | 0.5 mg/kg | 1.0 mg/kg | 0.5/1.0 mg/kg | 2.0 mg/kg |
| | (N=524) | (N=337) | (N=329) | (N=666) | (N=141) |
| Population | n (%) | n (%) | n (%) | n (%) | n (%) |
| All Randomized | 524 (100.0) | 337 (100.0) | 329 (100.0) | 666 (100.0) | 141 (100.0) |
| Safety | 524 (100.0) | 337 (100.0) | 329 (100.0) | 666 (100.0) | 141 (100.0) |
| Modified Intent-to-Treat (mITT) | 493 (94.1) | 314 (93.2) | 307 (93.3) | 621 (93.2) | 133 (94.3) |
| PiB PET | 15 (2.9) | 12 (3.6) | 12 (3.6) | 24 (3.6) | 3 (2.1) |
| CSF | 77 (14.7) | 47 (13.9) | 54 (16.4) | 101 (15.2) | 9 (6.4) |
| vMRI | 244 (46.6) | 169 (50.1) | 146 (44.4) | 315 (47.3) | 60 (42.6) |
| PK/PD | 10 (1.9) | 329 (97.6) | 319 (97.0) | 648 (97.3) | 140 (99.3) |

CSF = cerebrospinal fluid; PD = pharmacodynamic; PK = pharmacokinetic; PiB PET = Pittsburgh Compound B positron emission tomography; vMRI = volumetric magnetic resonance imaging.
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**Diagnosis and Main Criteria for Inclusion and Exclusion**: Subjects were enrolled in the study if they were 50 to <89 years of age; had a diagnosis of probable AD according to the National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association (NINCDS/ADRDA) criteria and a screening visit brain MRI scan consistent with a diagnosis of AD; had an MMSE score of 16 to 26 inclusive; had a Rosen Modified Hachinski Ischemic score ≤4; lived at home or independently in a community dwelling and had a reliable caregiver who consented to participate in the study, could accompany the subject on all clinic visits, and was a reliable informant in the opinion of the investigator; received stable doses of medication(s) for the treatment of nonexcluded medical condition(s) for at least 30 days prior to screening (concurrent treatment with cholinesterase inhibitors and/or memantine was allowed if the subject was maintained on a stable dose regimen for at least 120 days prior to screening, was free of any clinically significant side effects attributable to the drug,

and agreed [with caregiver agreement] that they would continue the same regimen for the duration of the trial); and were a noncarrier of *APOE*E4* as determined by genotyping.

Subjects were excluded if they had clinically significant neurological disease other than AD; a major psychiatric disorder; a history of stroke or seizures; a brain MRI scan indicative of significant non-AD abnormality; or a history or evidence of any clinically significant autoimmune disease or chronic illness which was likely to result in deterioration affecting the subject's safety during the study. Also excluded were subjects currently taking anticonvulsants, antiparkinsonian agents, antiplatelet agents for stroke prevention, anticoagulants, experimental medications for AD, recent immunosuppressive or cancer chemotherapy drugs, or cognitive enhancers other than acetylcholinesterase inhibitors or memantine; who discontinued cholinesterase inhibitors, memantine or cognitive enhancing agents within 60 days prior to screening; or who had a contraindication for brain MRI scan monitoring.

**Test Product, Dose and Mode of Administration, Batch No**: One of 2 dose levels of bapineuzumab (0.5- or 1.0-mg/kg) was administered by IV infusion every 13 weeks for a total of 6 infusions over the course of the study. It was provided in vials which allowed for withdrawal of 100 mg (20 mg/mL, ~5 mL) of the active compound. Infusions were performed over 60 ± 20 minutes via an infusion pump. Pfizer's drug product batch numbers 490601A, C42508, 0000056023, 0000060439, and F31676 were used during this study.

**Reference Therapy, Dose and Mode of Administration, Batch No**.: In North America, commercially available normal saline in infusion bags was used as placebo. In Europe, placebo kits (ampules), made of 0.9% saline were used (batch numbers 8141C11, 9152C13, and 11321013). Placebo was administered by IV infusion every 13 weeks for a total of 6 infusions over the course of the study and infusions were performed as described for bapineuzumab.

**Duration of Treatment**: The planned study duration was approximately 83 weeks, including a 6-week screening period, 65 weeks of dosing, and 13 weeks of follow-up.

**Criteria for Evaluation**: Key efficacy objectives and endpoints were evaluated using the ADAS-Cog/11 and DAD assessed at approximately 3-month intervals and the DS and CDR-SB assessed at approximately 6-month intervals. A minimum of 2 blinded raters at each site administered the efficacy scales. Key biomarker objectives and endpoints were evaluated in the following 3 optional substudies:

- **PET substudy**: PET imaging for brain amyloid burden using $^{11}$C-PiB was conducted in approximately 10% of enrolled subjects in the United States (US).
- **CSF substudy**: CSF p-tau concentrations were examined in approximately 20% of enrolled subjects in the US, Canada, Germany, and Austria.
- **Volumetric brain MRI substudy**: Volumetric brain MRIs were conducted at approximately one-half of the study centers located in the US and Canada.

Safety objectives and endpoints were assessed by monitoring TEAEs, vital signs, ECG parameters, clinical laboratory tests, brain MRI scans, physical and neurological examinations, infusion site assessments, and suicidality assessments.

**Statistical Methods**:

**Sample Size Determination**: Approximately 520 subjects were to be randomized to receive placebo and 390 subjects were to be randomized to each of the bapineuzumab dose groups (0.5- and 1.0-mg/kg). This gave 90% power to detect a 2.65 unit advantage for a bapineuzumab dose group over placebo on the ADAS-Cog/11 total score and a 6.56 unit advantage on the DAD total score, at the primary time point

(Week 78). The standard deviations were estimated from previous bapineuzumab studies (9.3 for the ADAS-Cog/11 and 23.0 for the DAD).

**Planned Analyses**

Primary Efficacy Analyses

The change from baseline ADAS-Cog/11 total score and DAD total score were analyzed using a restricted maximum likelihood (REML)-based mixed model for repeated measures (MMRM). The response variable was the change from baseline to each postbaseline visit. The model included the following fixed effects: treatment with 3 levels (0.5-mg/kg and 1.0-mg/kg bapineuzumab, and placebo), scheduled visit (a categorical factor), treatment-by-visit interaction, baseline (a continuous covariate), baseline-by-visit interaction, baseline MMSE total score stratum, baseline cholinesterase inhibitor or memantine use stratum, and baseline age (a continuous covariate).

The primary analysis was based on the treatment difference estimated at Week 78 using least-squares means with factor levels weighted according to overall baseline sample proportions.

Key Clinical Secondary Analyses

*Time to First Clinically Meaningful Deterioration*

For the US analysis, the "time to first clinically meaningful deterioration" was defined using fixed cut-off points for ADAS-Cog/11 total score (≥7 points) and the DAD total score (≥12 points). For the European Union (EU) analysis, the "time to first clinically meaningful deterioration" was defined using the study placebo median as the cut-off point (instead of a fixed cut-off point) (see SAP). Time to first clinically meaningful deterioration was summarized using descriptive statistics and Kaplan-Meier curves, and was analyzed using a log-rank test stratified by baseline MMSE total score stratum and baseline cholinesterase inhibitor or memantine use stratum.

*Dependence Scale*

The change in DS total score was analyzed using the same MMRM as described for the primary analyses.

Key Biomarker Secondary Analyses

*Brain Amyloid Burden Assessed by PiB PET*

Change in $^{11}$C-PiB PET GCA SUVr from baseline to Week 71 was analyzed using a similar MMRM as described for the primary analyses.

*Phosphorylated Tau Concentrations in CSF*

Change in CSF p-tau from baseline to Week 71 was analyzed using an analysis of covariance (ANCOVA) model with terms for treatment, baseline, baseline MMSE total score stratum, baseline cholinesterase inhibitor or memantine use stratum, and baseline age.

*Cerebral Atrophy by vMRI BBSI*

Brain boundary shift integral was analyzed using a similar MMRM as described for the primary analyses but with baseline whole brain volume (WBV) used as a continuous covariate (as there was no baseline BBSI value). The primary analysis was based on the treatment differences estimated at Week 71.

Key Divergence of Effect Secondary Analyses

Within the MMRMs for ADAS-Cog/11 and DAD total score for the primary analyses, linear contrasts were formed to estimate the slopes from Week 39 (the 9-month visit) through Week 78 (the 18-month visit) of the modeled differences between each bapineuzumab group and placebo for each variable. Positive divergence of effect was based on a statistically significant slope favoring bapineuzumab.

Subgroup Analyses of Subjects With Mild AD

Treatment differences were explored in subjects with mild AD by repeating the coprimary, key secondary, and secondary analyses in this subgroup. Mild AD was defined as baseline MMSE total score ≥21 and alternative baseline MMSE cutpoints (≥20 and ≥22) were also used for exploratory analyses.

Secondary Analyses

*Global Clinical Assessment*

The change in CDR-SB total score was analyzed using the same MMRM as described for the primary analyses.

*Responder Analyses*

For the US analysis, an ADAS-Cog/11 responder was defined as a subject with a worsening from baseline to Week 78 of <7 points on the ADAS-Cog/11; and a DAD responder was defined as a subject with a worsening from baseline to Week 78 of <12 points on the DAD. Differences in percent of responders between both active treatment groups and placebo on the ADAS-Cog/11 total score and DAD total score were evaluated using a Cochran-Mantel-Haenszel test stratified by the baseline MMSE total score stratum and the baseline cholinesterase inhibitor or memantine use stratum. For the EU analysis, the proportions of subjects with worsening from baseline to Week 78 in ADAS-Cog/11 total score of ≤ 0, ≤ 3, and ≤ 7 points and DAD total score of ≤ 0, ≤ 6, and ≤ 12 points were summarized.

Safety Analyses

Adverse events were classified into standard terminology using the Medical Dictionary for Regulatory Activities (MedDRA) version 14.1. Treatment-related AEs were summarized separately from all AEs and the maximum severity of AEs was summarized. Other safety variables (eg, vital signs, ECG parameters, and clinical laboratory tests) were also summarized.

**RESULTS**

**Study Population**: Of the 1331 subjects in the all randomized analysis population, 932 (70.0%) completed the study: 373 (71.2%) subjects in the placebo group and 238 (70.6%), 226 (68.7%), and 95 (67.4%) subjects in the bapineuzumab 0.5-, 1.0-, and 2.0-mg/kg groups, respectively. The most common reasons for early termination were adverse events (bapineuzumab 0.5-mg/kg, 9.2%; bapineuzumab 1.0-mg/kg, 7.5%; bapineuzumab 2.0-mg/kg, 12.0%; placebo, 6.9%) and withdrawal by subject (bapineuzumab 0.5-mg/kg, 8.0%; bapineuzumab 1.0-mg/kg, 12.7%; bapineuzumab 2.0-mg/kg, 6.8%; placebo, 9.9%).

In the mITT analysis population, the majority of subjects were white (94.9%), female (53.2%), and ≥65 years of age (77.5%). The mean age was approximately 73 years, ranging from 50 to 88 years. The mean duration of AD was 3.1 years. Approximately 90% of subjects used a cholinesterase inhibitor or memantine at baseline based on the randomization stratification factor. Approximately 51% of subjects had a baseline MMSE total score ≤21 (ie, mild AD based on randomization stratification factor). All of these factors were fairly balanced between the placebo and bapineuzumab groups.

Major protocol deviations were composed mainly of rater deviations, missing data, and ICF deviations. Site [redacted] violated good clinical practices (GCP) and there was suspicion that the majority of subjects may not have met probable AD criteria. Therefore, data from all 23 subjects randomized at this site was excluded from efficacy, health outcome, and PK/PD analyses.

Among subjects in the safety analysis population, 70.0% in the placebo group and 67.4%, 61.7%, and 61.7% in the bapineuzumab 0.5-, 1.0-, and 2.0-mg/kg groups received all 6 infusions. The median exposure to study drug was 1.49 years in all 4 treatment groups.

**Efficacy Results**: Efficacy analyses were performed on the appropriate populations shown in Table S-1 above. Because of the discontinuation of the bapineuzumab 2.0-mg/kg dose group, only descriptive summaries of efficacy data is provided for this treatment group.

The results of this study showed there was no difference between the placebo and bapineuzumab 0.5- or 1.0-mg/kg treatment groups with respect to the coprimary endpoints of change from baseline to Week 78 in ADAS-Cog/11 total score and change from baseline to Week 78 in DAD total score (Table S-2). A subgroup analysis by disease severity showed no treatment differences in the coprimary efficacy endpoints for subjects with either mild or moderate AD.

**Table S-2 Efficacy Results for Coprimary Endpoints (mITT Analysis Population)**

| | Placebo | Bapineuzumab | | |
|---|---|---|---|---|
| | | | | Pooled |
| | | 0.5 mg/kg | 1.0 mg/kg | 0.5/1.0 mg/kg |
| | (N=493) | (N=314) | (N=307) | (N=621) |
| **ADAS-Cog/11 Total Score** | | | | |
| Change From Baseline to Week 78: MMRM Analysis | | | | |
| LS Mean (SE) | 7.4 (0.46) | 7.1 (0.58) | 7.8 (0.59) | 7.5 (0.41) |
| Difference of LS Means (95% CI) | | -0.3 (-1.8, 1.1) | 0.4 (-1.1, 1.8) | 0.0 (-1.2, 1.2) |
| p-value | | 0.642 | 0.620 | 0.994 |
| **DAD Total Score** | | | | |
| Change From Baseline to Week 78: MMRM Analysis | | | | |
| LS Mean (SE) | -15.5 (0.96) | -12.7 (1.20) | -14.6 (1.23) | -13.7 (0.86) |
| Difference of LS Means (95% CI) | | 2.8 (-0.2, 5.8) | 0.9 (-2.1, 4.0) | 1.9 (-0.6, 4.4) |
| p-value | | 0.067 | 0.550 | 0.143 |

ADAD-Cog = Alzheimer's Disease Assessment Scale – Cognitive subscale, CI = confidence interval; DAD = Disability Assessment for Dementia; LS = least-squares; MMRM = mixed model for repeated measures; SE = standard error.
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The study also showed that the placebo and bapineuzumab groups had similar times to clinically meaningful deterioration. For the ADAS-Cog/11 total score, the Kaplan-Meier estimate of median time to a worsening of ≥7 points was 553 days for the placebo group and 552 days for the bapineuzumab 0.5-mg/kg (p=0.962) and 1.0-mg/kg (p=0.310) groups, while the Kaplan-Meier estimate of the median

time to median placebo deterioration was 542 days for the placebo group, 544 days for the bapineuzumab 0.5-mg/kg group (p=0.644), and 476 days for the bapineuzumab 1.0-mg/kg group (p=0.339). For the DAD total score, the Kaplan-Meier estimate of median time to a worsening of ≥12 points was 547 days for the placebo group, 548 days for the bapineuzumab 0.5-mg/kg group (p=0.389), and 549 days for the bapineuzumab 1.0-mg/kg group (p=0.491), while the Kaplan-Meier estimate of the median time to median placebo deterioration was 465 days for the placebo group, 544 days for the bapineuzumab 0.5-mg/kg group (p=0. 449), and 470 days for the bapineuzumab 1.0-mg/kg group (p=0.822).

No divergence of effect was noted between the placebo and bapineuzumab groups based on MMRM analysis of the estimated slope in ADAS-Cog/11 and DAD total scores from Week 39 through Week 78. The difference between the placebo and bapineuzumab 0.5-mg/kg groups was 0.0 units/year (95% CI: -1.4, 1.4; p=0.988) for the ADAS-Cog/11 total score and 3.5 units/year (95% CI: 0.5, 6.5; p=0.022) for the DAD total score, while the estimated slopes of the difference between the placebo and bapineuzumab 1.0-mg/kg groups for the ADAS-Cog/11 and DAD total scores were 0.0 units/year (95% CI: -1.4, 1.5; p=0.945) and 0.8 units/year (95% CI: -2.3, 3.8; p=0.624), respectively.

There were no differences between the treatment groups in the dependence on caregivers (as measured by the DS total score). At Week 78, the difference in the LS mean change (based on MMRM analysis) in the DS total score was -0.1 (95% CI: -0.4, 0.3), p=0.742 for the bapineuzumab 0.5-mg/kg group and 0.1 (95% CI: -0.2, 0.5), p=0.464 for the bapineuzumab 1.0-mg/kg group.

Changes from baseline in PiB PET GCA SUVr or CSF p-tau did not show statistically significant differences from placebo for the pooled bapineuzumab 0.5/1.0-mg/kg treatment group (primary comparison), nor were the changes in vMRI BBSI (brain volume) statistically different from placebo for the bapineuzumab 0.5- or 1.0-mg/kg groups (primary comparisons) (Table S-3). Subgroup analyses by disease severity showed a similar pattern of results for each of the key biomarker endpoints.

**Table S-3 Efficacy Results for Key Biomarker Secondary Endpoints**

| | Placebo | Bapineuzumab | | |
|---|---|---|---|---|
| | | | | Pooled |
| | | 0.5 mg/kg | 1.0 mg/kg | 0.5/1.0 mg/kg |
| **PiB PET GCA SUVr (PiB PET Analysis Population)** | | | | |
| Change From Baseline to Week 71: MMRM Analysis | | | | |
| N[a] | 15 | 12 | 12 | 24 |
| LS Mean (SE) | -0.046 (0.0443) | 0.039 (0.0452) | -0.094 (0.0471) | -0.025 (0.0337) |
| Difference of LS Means (95% CI) | | 0.085 (-0.046, 0.215) | -0.048 (-0.182, 0.086) | 0.021 (-0.099, 0.140) |
| p-value | | 0.193 | 0.466 | 0.724 |
| **CSF p-tau (CSF Analysis Population)** | | | | |
| Change From Baseline to Week 71: ANCOVA Analysis | | | | |
| N[a] | 77 | 47 | 54 | 101 |
| LS Mean (SE) | -1.98 (1.478) | -1.93 (1.911) | -8.17 (1.803) | -5.23 (1.330) |
| Difference of LS Means (95% CI) | | 0.05 (-4.78, 4.88) | -6.19 (-10.82, -1.56) | -3.30 (-7.30, 0.71) |
| p-value | | 0.984 | 0.009 | 0.106 |
| **vMRI BBSI (vMRI Analysis Population)** | | | | |
| Shift From Baseline to Week 71: MMRM Analysis | | | | |
| N[a] | 244 | 169 | 146 | 315 |
| LS Mean (SE) | 17.521 (0.6126) | 17.184 (0.7337) | 19.035 (0.7941) | 18.041 (0.5402) |
| Difference of LS Means (95% CI) | | -0.336 (-2.216, 1.543) | 1.514 (-0.459, 3.487) | 0.516 (-1.093, 2.126) |
| p-value | | 0.725 | 0.132 | 0.529 |

a. Total number of subjects in the individual analysis population

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**Pharmacokinetics and Pharmacodynamic Results**: The majority of subjects in all 3 bapineuzumab treatment groups maintained detectable serum concentrations through Week 78. Mean serum bapineuzumab concentrations at the end of the first infusion increased in an approximate dose-proportional manner in the bapineuzumab 0.5-, 1.0-, and 2.0-mg/kg groups on Day 1 (12125, 23132, and 44707 ng/mL, respectively). Results from the PK/PD/ECG substudy indicated dose proportionality in both $C_{max}$ and $AUC_{inf}$ across the dose range from 0.5-mg/kg to 2.0-mg/kg. Mean accumulation ratios, measured by ratio of $AUC_{inf}$ after the third and first infusions ranged from 1.2 to 1.4, suggesting minimum accumulation with the every 13-week dosing regimen. Mean clearance values after the third infusion were consistent across the dose levels tested: 0.089, 0.077, and 0.090 mL/h/kg for the 0.5-, 1.0-, and 2.0-mg/kg groups, respectively. In the CSF analysis population, bapineuzumab crossed the blood brain barrier following IV administration (mean CSF:serum ratios at Week 71 of 0.0027, 0.0034, and 0.0025 for the bapineuzumab 0.5-, 1.0-, and 2.0-mg/kg groups, respectively). Plasma $A\beta_{x-40}$ concentrations increased following the IV administration of bapineuzumab and were approximately

proportional to the serum bapineuzumab concentration. There were no significant changes from baseline in CSF $A\beta_{x-40}$ and $A\beta_{x-42}$ at Week 71.

**Medical Resource Utilization and Health Economics Results:** There were no significant differences between groups in measures of health economics or medical resource utilization, consistent with the lack of efficacy demonstrated in this study.

**Safety Results:**

Infusion of bapineuzumab 0.5- or 1.0-mg/kg every 13 weeks was generally well tolerated, with similar percentages of subjects in placebo and bapineuzumab 0.5- and 1.0-mg/kg treatment groups having at least 1 treatment-emergent adverse event (TEAE), a serious TEAE(s), or a TEAE(s) that led to study drug discontinuation (Table S-4). The frequencies of serious TEAEs or TEAEs leading to study drug discontinuation that were assessed as related to study drug by the Investigator, while low, were higher in the bapineuzumab 0.5- and 1.0-mg/kg groups compared to the placebo group (Table S-4). In the bapineuzumab 2.0-mg/kg group, the proportions of subjects with serious TEAEs (any or related) and TEAEs leading to discontinuation of study drug (any or related) were higher than for the 0.5- and 1.0-mg/kg groups.

Across all treatment groups, 23 subjects had a TEAE with a fatal outcome. For 3 of these subjects, the fatal TEAE was assessed as related to study drug ([redacted] in the 0.5-mg/kg group and [redacted] in the 2.0-mg/kg group).

**Table S-4 Overview of Adverse Events (Safety Analysis Population)**

| | Placebo | Bapineuzumab | | |
|---|---|---|---|---|
| | (N=524) n (%) | 0.5 mg/kg (N=337) n (%) | 1.0 mg/kg (N=329) n (%) | 2.0 mg/kg (N=141) n (%) |
| Number of subjects with: | | | | |
| One or more TEAEs | 465 (88.7) | 299 (88.7) | 292 (88.8) | 128 (90.8) |
| One or more TEAEs related to study drug | 95 (18.1) | 72 (21.4) | 92 (28.0) | 38 (27.0) |
| One or more serious TEAEs | 108 (20.6) | 72 (21.4) | 76 (23.1) | 38 (27.0) |
| One or more serious TEAEs related to study drug | 8 (1.5) | 12 (3.6) | 13 (4.0) | 10 (7.1) |
| TEAE with a fatal outcome | 7 (1.3) | 4 (1.2) | 7 (2.1) | 5 (3.5) |
| Early termination of study drug due to TEAEs | 41 (7.8) | 31 (9.2) | 26 (7.9) | 19 (13.5) |
| Early termination of study drug due to related TEAEs | 6 (1.1) | 10 (3.0) | 13 (4.0) | 10 (7.1) |

Notes:
1. Each AE was classified by the investigator as "Related" or "Not Related" on the CRF and that classification is used for this table. AEs with missing relatedness are counted as "Related".
2. Counts and percentages are based on the number of subjects with AEs (not events).
3. An AE will be regarded as treatment-emergent if it started during or after the first infusion of study drug and prior to or on the date of last dose + 137 days.
Source: Q:\Projects\AAB001\301\Final\table\program\t_oae_top_t.sas [19JUL2012 15:06]

The TEAEs that occurred in ≥10% of subjects in any treatment group are summarized in Table S-5. A clear dose-related trend was seen for vasogenic cerebral edema (hereafter referred to as ARIA-E [VE]). The serious TEAEs that occurred in >1% of subjects in any bapineuzumab treatment group were as follows: vasogenic cerebral edema (0.0%, 1.5%, 1.5%, and 5.0% in placebo, bapineuzumab 0.5-, 1.0-, and

2.0-mg/kg groups, respectively), syncope (1.0%, 1.2%, 1.2%, and 2.8%, respectively), convulsion (0.8%, 0.3%, 1.8%, and 1.4%, respectively), diverticulitis (0.2%, 0.0%, 1.2%, and 0.7%, respectively), hip fracture (0.4%, 1.2%, 1.2%, and 0.0%, respectively), pneumonia (1.5%, 0.9%, 2.4%, and 0.7%, respectively), agitation (0.6%, 0.3%, 0.0%, and 1.4%, respectively), and angina pectoris (0.0%, 0.3%, 0.3%, and 2.1%, respectively).

There was no evidence for hypersensitivity, hepatotoxicity, bone marrow toxicity, severe cutaneous reactions, or cardiac conduction abnormalities associated with bapineuzumab administration, and the occurrence of ischemic stroke was similar among all treatment groups while the occurrence of cancer (neoplasms system organ class and cancers other squamous cell carcinoma/basal cell carcinoma) was not higher in the bapineuzumab groups compared to placebo.

**Table S-5 Treatment-Emergent Adverse Events That Occurred in at Least 10% of Subjects in Any Treatment Group (Safety Analysis Population)**

| | Placebo | Bapineuzumab | | |
|---|---|---|---|---|
| **Body System Preferred Term** | **(N=524) n (%)** | **0.5 mg/kg (N=337) n (%)** | **1.0 mg/kg (N=329) n (%)** | **2.0 mg/kg (N=141) n (%)** |
| **Nervous system disorders** | 204 (38.9) | 124 (36.8) | 144 (43.8) | 67 (47.5) |
| Headache | 49 (9.4) | 30 (8.9) | 34 (10.3) | 16 (11.3) |
| Vasogenic cerebral oedema | 1 (0.2) | 14 (4.2) | 31 (9.4) | 20 (14.2) |
| **Infections and infestations** | 189 (36.1) | 108 (32.0) | 119 (36.2) | 50 (35.5) |
| Urinary tract infection | 59 (11.3) | 40 (11.9) | 42 (12.8) | 15 (10.6) |
| **Psychiatric disorders** | 178 (34.0) | 102 (30.3) | 106 (32.2) | 55 (39.0) |
| Anxiety | 43 (8.2) | 19 (5.6) | 39 (11.9) | 11 (7.8) |
| Depression | 58 (11.1) | 27 (8.0) | 19 (5.8) | 11 (7.8) |
| Agitation | 37 (7.1) | 26 (7.7) | 15 (4.6) | 16 (11.3) |
| **Injury, poisoning and procedural complications** | 135 (25.8) | 88 (26.1) | 93 (28.3) | 37 (26.2) |
| Fall | 73 (13.9) | 43 (12.8) | 43 (13.1) | 23 (16.3) |
| **Vascular disorders** | 80 (15.3) | 38 (11.3) | 34 (10.3) | 22 (15.6) |
| Hypertension | 54 (10.3) | 24 (7.1) | 21 (6.4) | 10 (7.1) |

Notes:

1. Counts and percentages are based on the number of subjects with AEs (not events).
2. Adverse events are coded using MedDRA version 14.1.
3. An AE will be regarded as treatment-emergent if it started during or after the first infusion of study drug and prior to or on the date of last dose + 137 days.

Source: Q:\Projects\AAB001\301\Final\table\program\t_ae_top_t.sas [19JUL2012 15:04]

ARIA-E (VE) was the most notable TEAE in the bapineuzumab groups. A review of all interpretable MRI scans from subjects who received at least part of 1 dose of study drug and who had completed study was conducted by a separate and independent group of neuroradiologists who were blinded to subject's clinical history and treatment. Based on this review, hereafter referred to as MRI Final Read, the incidence proportion of treatment-emergent ARIA-E (VE) was 0.6% in the placebo group, 5.6% in the bapineuzumab 0.5-mg/kg group, 13.4% in the bapineuzumab 1.0-mg/kg group, and 19.9% in the

bapineuzumab 2.0-mg/kg group. Bapineuzumab dose level (ie, higher doses) was shown to be a significant risk factor for ARIA-E (VE) in a logistic regression analysis, and a dose-related trend was seen for ARIA-E (VE) in an analysis by absolute dose quartile for bapineuzumab.

Treatment-emergent ARIA-E (VE) tended to occur early during the course of bapineuzumab treatment with the majority of subjects in all treatment groups having this event between the first and third infusions. Among subjects with ARIA-E (VE), the median days to first onset suggested a dose-related trend (178.0, 136.0, 49.5, and 45.5 days for placebo and bapineuzumab 0.5-, 1.0-, and 2.0-mg/kg groups, respectively), with ARIA-E (VE) seen earlier as the dose of bapineuzumab increased. There was also a trend toward a shorter median duration of treatment-emergent ARIA-E (VE) as the dose of bapineuzumab increased (141.0, 108.0, and 91.0 days for resolved cases in the bapineuzumab 0.5, 1.0-, and 2.0-mg/kg groups, respectively).

The proportion of subjects with a first episode of treatment-emergent hemosiderin deposits (HDs) <10 mm after early infusions was greater than after late infusions for the bapineuzumab groups, following a similar time course pattern as for ARIA-E (VE). Total radiologic severity scores (a summation of scale scores [which range from 0 to 5] for parenchymal and sulcal hyperintensity and swelling, for the left and right side of each of 6 brain regions [frontal, temporal, parietal, occipital, cerebellum/ brainstem, and central brain]) also decreased over time in the bapineuzumab groups. The mean number of incident HD <10 mm (MRI Final Read) during an ARIA-E (VE) episode was greater than the mean number prior to onset of ARIA-E (VE) in the bapineuzumab 2.0-mg/kg (5.5 vs 0.7) and bapineuzumab 1.0-mg/kg (1.7 vs 0.4) groups. The occurrence of incident HDs <10 mm did not appear to increase once ARIA-E (VE) resolved. Mean maximum radiologic severity scores with ARIA-E (VE) for the bapineuzumab groups did not show a clear dose-related trend.

In the bapineuzumab 0.5- and 1.0-mg/kg groups, ARIA-E (VE) was generally asymptomatic (64.3% and 83.9%, respectively) and mild (57.1% and 61.3%, respectively), although the proportions of cases that were severe (35.0%) and symptomatic (55.0%) were higher in the bapineuzumab 2.0-mg/kg group. In all 3 bapineuzumab groups, the presence of ARIA-E (VE) did not appear to have any effect on cognitive or functional assessments, as determined by the mean changes in the MMSE, ADAS-Cog/11, and DAD total scores from the preceding visit to the visit indicating/following ARIA-E (VE).

Although study drug infusions were to have been withheld for the duration of the ARIA-E (VE) episode, dosing continued throughout the episode for 49 of the 94 (~52%) subjects with ARIA-E (VE) identified on the MRI Final Read. This was mainly due to the fact that ARIA-E (VE) was only detected during the MRI Final Read. There were generally no differences in outcomes (ie, mean number of HDs <10 mm, mean maximum total radiologic scores, parenchymal vasogenic edema, leptomeningeal vasogenic edema and swelling scores, infarcts, and severity of ARIA-E [VE]) between subjects who had the study drug withheld during ARIA-E (VE) episode and those who were dosed through the episode, other than duration, which was shorter for episodes that were not dosed through.

Recurrent episodes of ARIA-E (VE) occurred in 10 subjects across the bapineuzumab groups, including 9 which recurred after re-initiation of treatment and 1 which recurred spontaneously.

Regarding other events of special circumstance for bapineuzumab, seizure/convulsions also occurred at a higher incidence for bapineuzumab (0.3%, 2.1%, and 2.1% for 0.5-, 1.0-, and 2.0-mg/kg groups, respectively) compared to placebo (1.0%) in this study. The proportion of subjects with intracranial hemorrhage or deep vein thrombosis/pulmonary embolism did not significantly differ between the placebo and bapineuzumab 0.5- and 1.0-mg/kg groups, although intracranial hemorrhage was reported more often with bapineuzumab 2.0-mg/kg (2.8%) than with placebo (1.3%).

Changes from baseline in laboratory parameters were generally small and not considered clinically relevant. In general, there were no notable differences in vital signs or physical/neurological examinations between the placebo and bapineuzumab groups.

Based on ECG findings, there was no apparent difference between the placebo and bapineuzumab groups with respect to the percentage of subjects with clinically relevant (elevated) QTc intervals, either on routine ECGs performed for the entire safety analysis population or for more intensive ECG monitoring in the PK/PD/ECG substudy. Among the 45 subjects participating in the PK/PD/ECG substudy, 1 subject had a change in QTcB or QTcF values of ≥60 msec on a postdose ECG (change from baseline of 73 and 60 msec, respectively) and corresponding QTcB and QTcF values of 511 and 490 msec, respectively.

There were no anti-bapineuzumab antibodies detected in any serum or CSF samples, suggesting a low immunogenic potential for bapineuzumab. These results are consistent with similar observations from all previous clinical studies.

**Study Limitations:** The fewer than targeted subjects in the PiB PET substudy (N=39 versus target of 100) who did not have adequate amyloid at baseline (as determined by meeting a threshold of ≥1.35 GCA SUVr at baseline) coupled with not having enough subjects with postbaseline scans for various reasons was a limitation of this study.

**Conclusion(s):** Bapineuzumab IV was not clinically efficacious in this study in subjects with mild or moderate AD who were *APOE*E4* noncarriers. A clinically relevant increase in ARIA-E (VE) and a small increase in seizures as compared with placebo were the only notable safety concerns related to bapineuzumab treatment.

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