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GENERIC DRUG NAME / COMPOUND NUMBER: Bapineuzumab / AAB-001, ELN115727

PROTOCOL NO.: 3133K1-3001-WW/US (B2521002)

PROTOCOL TITLE: 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 Disease Who Are Apolipoprotein E ε4 Carriers

Study Centers: A total of 218 centers took part in the study and randomized subjects; 52 in the United States (US), 36 in Japan, 19 in France, 16 in Spain, 13 in the United Kingdom (UK), 10 each in the Netherlands and Italy, 7 in Australia, 6 each in South Africa, Belgium and Germany, 5 in Poland, 4 each in Argentina, Austria and Slovakia, 3 each in Portugal, Serbia and Switzerland, 2 each in Sweden, Mexico, New Zealand, Chile and Finland and 1 in Croatia.

Study Initiation and Final Completion Dates: 28 May 2008 to 03 December 2012. The study was terminated prematurely on 06 August 2012.

Please note that this study drug is no longer in development and is not available for prescribing.

Phase of Development: Phase 3

Study Objectives:

Primary Objective:

To demonstrate an advantage of the efficacy of multiple doses of intravenously (IV) administered bapineuzumab 0.5 mg/kg compared with placebo in subjects with mild to moderate Alzheimer's disease (AD) who were Apolipoprotein E ε4 (ApoE4) carriers, as measured by both of the following:

- The change from Baseline to Week 78 for the Alzheimer's Disease Assessment Scale - Cognitive Subscale, 11-item (ADAS-Cog/11) total score;
- The change from Baseline to Week 78 for the disability assessment for dementia (DAD) total score.

Secondary Objectives:

Biomarker Objectives: To evaluate the effect of multiple doses of IV administered bapineuzumab 0.5 mg/kg compared with placebo on biomarkers that could be indicative of disease progression in subsets of subjects with mild to moderate AD who were ApoE4 carriers. The following biomarkers were evaluated:

- The change from Baseline to Week 71 in brain amyloid burden (average standard uptake value ratio [SUVr] in prespecified regions of interest [ROIs]) assessed by ^{11}C-Pittsburgh compound B (PIB) positron emission tomography (PET) imaging in a subset of subjects;
- The change from Baseline to Week 71 in phospho-tau (p-tau) levels in the cerebrospinal fluid (CSF) in a subset of subjects;
- The change from Baseline to Week 71 in brain volume, assessed by magnetic resonance imaging (MRI) brain boundary shift integral (BBSI) in a subset of subjects.

Divergence of Effect Objectives: To demonstrate divergence of effect (increasing separation with time) on ADAS-Cog/11 and DAD with multiple doses of IV administered bapineuzumab 0.5 mg/kg compared with placebo in subjects with mild to moderate AD who were ApoE4 carriers, evaluating:

- Divergence of effect on the ADAS-Cog/11 total scores from Week 39 to Week 78 between bapineuzumab and placebo;
- Divergence of effect on the DAD total scores from Week 39 to Week 78 between bapineuzumab and placebo.

Clinical and Health Outcomes Objectives: To demonstrate the effect of multiple doses of IV administered bapineuzumab 0.5 mg/kg compared to placebo on time to progression in subjects with mild to moderate AD who were ApoE4 carriers, where time to progression endpoints were:

- Time to median placebo deterioration on ADAS-Cog/11 total score versus median bapineuzumab deterioration;
- Time to median placebo deterioration on DAD total score versus median bapineuzumab deterioration.

To evaluate the effect of multiple doses of IV administered bapineuzumab 0.5 mg/kg compared with placebo on subject dependence in subjects with mild to moderate AD who were ApoE4 carriers, determined by the change from Baseline to Week 78 in the total dependence scale (DS) scores.

Other Secondary Objectives: To demonstrate the effect of multiple doses of IV administered bapineuzumab 0.5 mg/kg compared to placebo on the proportion of responders in subjects with mild to moderate AD who were ApoE4 carriers based on:

- Proportions of subjects with worsening from Baseline to Week 78 of at most 0, 3 and 7 points on the ADAS-Cog/11 total score;
- Proportions of subjects with worsening from Baseline to Week 78 of at most 0, 6, and 12 points on the DAD total score;
- ADAS-Cog/11 total score cumulative response curves (reverse cumulative distribution functions);
- DAD total score cumulative response curves (reverse cumulative distribution functions).

To demonstrate the effect of multiple doses of IV administered bapineuzumab 0.5 mg/kg compared to placebo on a global clinical assessment in subjects with mild to moderate AD who were ApoE4 carriers, assessed by the change from Baseline to Week 78 score for the clinical dementia rating sum of boxes (CDR-SOB).

METHODS

Study Design: This was a multicenter, randomized, double-blind, placebo-controlled, parallel-group, outpatient study in male and female subjects with mild to moderate AD who were ApoE4 carriers. Subjects who met eligibility criteria were randomly assigned to receive either bapineuzumab 0.5 mg/kg or placebo by IV infusion every 13 weeks, for a total of 6 infusions over the course of the study. Subjects were enrolled in a 3:2 ratio of bapineuzumab 0.5 mg/kg to placebo. Subjects were stratified according to Mini-mental state examination (MMSE) score (16-21; 22-26), concomitant cholinesterase inhibitor and/or memantine use (yes; no), number of copies of ApoE4 (1 allele; 2 alleles), and participation in the optional substudies (PET and volumetric MRI [vMRI] alone or with CSF, CSF alone or with vMRI, vMRI alone, or none). This study was planned to be completed in approximately 48 months. On 06 August 2012, the Sponsor made the decision to terminate all ongoing bapineuzumab IV studies in subjects with mild to moderate AD due to the lack of clinical benefit seen in 2 completed bapineuzumab Phase 3 studies, therefore, both 3133K1-3001-WW and 3133K1-3001-US were terminated earlier than planned. The overall schedule of assessments is outlined in Table 1 and an additional schedule of events for CSF substudy subjects only is provided in Table 2.

Table 1. Subject Evaluation Schedule/Schedule of Activities

Study Period	Screen		Study Week (±3 Days)				Study Week (±7 Days)								
Procedures	**D -42 to D -4**	**Pre-D1**	**D1**	**W6**	**W13[a]**	**W19**	**W26[a]**	**W32**	**W39[a]**	**W45**	**W52[a]**	**W58**	**W65[a]**	**W71**	**W78/EW[b]**
Informed consent	X	X[c]													
Demography/medical history/prior medications	X														
Inclusion/exclusion criteria	X		X												
NINCDS-ADRDA and DSM-IV-TR criteria review	X														
MMSE	X			X		X		X		X		X			X
Rosen modified Hachinski ischemic score	X														
NTB, DAD, and ADAS-Cog[a]		X			X		X		X		X		X		X
CDR-SOB and NPI[a]		X					X				X				X
DS, RUD-Lite v2.4, QOL-AD, and HUI[a]		X					X				X				X
Clinical/volumetric MRIs[d]	X			X		X		X		X		X		X	X[e]
Physical examination[f]	X		X		X		X		X		X		X		X
Neurologic examination	X		X	X	X	X	X		X		X		X		X
12-Lead ECG	X									X					X
Vital signs[g,h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood chemistry, hematology, and urinalysis	X[i]		X	X		X		X		X		X		X	X
Apolipoprotein E ε4 genotyping	X														
Serum anti-bapineuzumab antibody			X[j,k]				X[j]								X
Serum bapineuzumab (PK)			X[l]	X			X[j,l]							X	X
Infusion[m]			X		X		X		X		X		X		
Assessment of infusion site[n]			X		X		X		X		X		X		
Postinfusion phone contact (~24 hours after infusion)			X		X		X		X		X		X		
Suicidality assessment	X	X[o]		X	X	X	X	X	X	X	X	X	X	X	X
AEs/concomitant medications		X	X	X	X	X	X	X	X	X	X	X	X	X	X
CSF substudy sample collection (CSF and blood)[p]		X[q]												X	X[e]

Table 1. Subject Evaluation Schedule/Schedule of Activities

PIB PET imaging[r, s]		X[t]								X[u]				X[u]	X[e]
Urine pregnancy test[v]		X								X				X	X[e]

ADAS-Cog = Alzheimer's Disease Assessment Scale–Cognitive Subscale; AE = adverse event; CDR-SOB = Clinical Dementia Rating Sum of Boxes; CSF = cerebrospinal fluid; D = day; DAD = Disability Assessment for Dementia; DS = dependence scale; DSM-IV-TR = Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition-Text Revision; ECG = electrocardiogram; EW = early withdrawal; HUI = Health Utilities Index; MMSE = mini-mental state examination; MRI = magnetic resonance imaging; NINCDS-ADRDA = National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association; NPI = neuropsychiatric inventory; NTB = neuropsychological test battery; PET = positron emission tomography; PIB = ^{11}C-Pittsburgh Compound B; PK = pharmacokinetics; QOL-AD = Quality of Life–Alzheimer's Disease; RUD-Lite v2.4 = Resource Utilization in Dementia, version 2.4; vMRI = volumetric magnetic resonance imaging; W = week.

a. Cognitive, functional, and health outcome assessments scheduled to be performed at infusion visits were done on a day prior to the infusion visit within the applicable visit window; if done on the same day as the infusion, they were done prior to all other procedures.
b. Week 78 was also the Screening Visit for subjects who transitioned to the extension study.
c. For sites using 2-step consent (screening and protocol specific consent forms).
d. For each MRI scan, the local and central radiology reports were available and reviewed by the Investigator prior to each study drug infusion. vMRI scans were obtained for subjects participating in the optional vMRI substudy. vMRI substudy subjects did not receive their next dose until the MRI scan had been received and accepted for volumetric analysis as confirmed by the MRI central vendor. vMRI substudy subjects were required to repeat MRI when a scan was unsatisfactory for volumetric analysis.
e. PET imaging (and associated pregnancy testing) and CSF collection at Week 78/EW refer only to subjects who withdrew from the study early, and only if the subject was participating in the associated substudy. MRI at Week 78/EW refers only to subjects who withdrew from the study early.
f. The physical examination at the Screening Visit and W78/EW was a full physical examination. For all other visits, the physical examination was a targeted examination.
g. Vital sign measurements at Screening included height and weight; vital signs at subsequent visits excluding Day 1 included weight. Day 1 weight was only required if the subject weight is not obtained at the preDay 1 visit.
h. Sitting vital sign measurements were taken at non-infusion visits. For Infusion Visits: Supine blood pressure and pulse were taken within 1 hour before dose administration and at approximately 15, 30, 60 (end of infusion), and 120 minutes after the start of infusion. Temperature and respiratory rate were taken within 1 hour before dose administration, and at approximately 60 (end of infusion) and 120 minutes after the start of infusion. For Day 1 and Week 13, vital signs were also measured at approximately 240 minutes (4 hours) after the start of infusion.
i. At the Screening Visit only, thyroid stimulating hormone, vitamin B_{12}, international normalized ratio for prothrombin time, and activated partial thromboblastin time were measured.
j. Blood sample was collected just prior to study drug infusion.
k. At the Day 1 visit, this sample was collected only for subjects who were not participating in the CSF substudy (this sample was collected, instead, at preDay 1 for CSF substudy subjects per Table 2).
l. Blood sample was collected immediately at the end of study drug infusion.
m. Subjects were monitored for any signs of immune-mediated events during and immediately following each infusion.
n. The infusion site was assessed before dose administration and 1 hour and 2 hours after the start of infusion. For the first 2 doses (Day 1 and Week 13), the infusion site was assessed 4 hours after the start of infusion.

Table 1. Subject Evaluation Schedule/Schedule of Activities

o. Suicidality assessment was performed at preDay 1 if >7 days since the Screening Visit assessment.
p. CSF and blood were collected only if the subject was participating in the optional substudy (see Table 2).
q. The preDay 1 CSF and associated blood samples might be collected at any point in the Screening Period after the subject has satisfied all entry criteria for the study.
r. Brain PIB PET imaging was performed only if the subject was participating in the optional substudy.
s. The PET scan schedule may have been modified locally to decrease the number of required scans to ensure compliance with local radiation safety requirements. The schedule provided in the flowchart for PIB PET scans represents the maximum number of scans that each subject received. Details regarding local modifications to the PET scanning schedule were provided in the PET imaging guidelines.
t. The preDay 1 PIB PET scan was performed at any point in the Screening Period after the subject had satisfied all entry criteria for the study and the site had received confirmation that the Screening vMRI scan was suitable for PIB PET participation. It was recommended that confirmation be received that the preDay 1 PIB PET scan was acceptable for analysis prior to randomizing the subject into the study.
u. The window for the PIB PET scan for this visit was ±14 days.
v. Urine pregnancy test required only for female subjects aged <55 years who participated in the PET substudy. Pregnancy test was to be performed prior to each PET scan.

Table 2. Additional Schedule of Events for CSF Substudy Subjects Only

Visit Description	CSF Tests	Blood Tests	CSF Local Laboratory Tests
PreDay 1	Anti-bapineuzumab antibodies (CSF, serum) Amyloid-beta protein (CSF, plasma) Total tau Phospho-tau	Anti-bapineuzumab antibodies (CSF, serum) Amyloid-beta protein (CSF, plasma)	Glucose, protein, WBCs, RBCs
Week 71	Bapineuzumab Anti-bapineuzumab antibodies (CSF, serum) Amyloid-beta protein (CSF, plasma) Total tau Phospho-tau	Anti-bapineuzumab antibodies (CSF, serum) Amyloid-beta protein (CSF, plasma)	Glucose, protein, WBCs, RBCs

CSF = cerebrospinal fluid; RBC = red blood cell; WBC = white blood cell.

Number of Subjects (Planned and Analyzed): A total of 1100 subjects were planned to participate in the study. The numbers of subjects planned to enroll in each substudy were as follows:

CSF substudy: Approximately 120 subjects in the placebo group and 180 subjects in the bapineuzumab group at a subset of study sites (approximately 300 subjects total).

Brain vMRI substudy: Approximately 272 subjects in the placebo group and 408 subjects in the bapineuzumab group at a subset of study sites (approximately 680 subjects total).

Brain PIB PET substudy: Approximately 32 subjects in the placebo group and 48 subjects in the bapineuzumab group at a subset of study sites (approximately 80 subjects total). Subjects in this substudy also participated in the brain vMRI substudy.

A total of 1099 subjects were randomized (658 in the bapineuzumab group and 441 in the placebo group). A total of 1093 were included in the safety population (654 in the bapineuzumab group; 439 in the placebo group) and 1081 in the modified intent-to-treat (mITT) population (650 in the bapineuzumab group; 431 in the placebo group).

Diagnosis and Main Criteria for Inclusion: Male and female subjects aged between 50-88 years with a diagnosis of probable AD, with an MMSE score of 16-26, brain MRI consistent with the diagnosis of AD, genetic testing confirming the presence of 1 or 2 copies of the ApoE4 allele, and a caregiver willing to participate and able to attend clinic visits with the subject were included in the study. Concurrent use of a cholinesterase inhibitor and/or memantine was allowed, if the dosing was stable.

Exclusion Criteria: Subjects with significant neurological disease other than AD, or a major psychiatric disorder, contraindication to undergo brain MRI (eg, pacemaker, CSF shunt, or foreign metal objects in the body) and women of childbearing potential were excluded.

Study Treatment: Bapineuzumab and placebo vials were supplied by the Sponsor. Bapineuzumab was supplied in single-use vials containing 100 mg of bapineuzumab. Placebo for bapineuzumab was supplied in single-use vials (or ampoules) containing sterile, preservative-free 0.9% sodium chloride (saline) solution. Subjects were randomly assigned to receive either bapineuzumab 0.5 mg/kg or placebo by IV infusion every 13 weeks, for a total of 6 infusions over the course of the study.

Efficacy Endpoints:

Primary Endpoints:

- Changes in ADAS-Cog/11 total score from Baseline to Week 78;
- Changes in DAD total score from Baseline to Week 78.

Secondary Endpoints:

- The change from Baseline to Week 71 in brain amyloid burden assessed by PIB PET imaging in a subset of subjects;
- The change from Baseline to Week 71 in p-tau levels in the CSF in a subset of subjects;
- The change from Baseline to Week 71 in brain volume, assessed by MRI BBSI in a subset of subjects;
- Divergence of effect on the ADAS-Cog/11 total scores from week 39 to Week 78 between bapineuzumab and placebo;
- Divergence of effect on the DAD total scores from Week 39 to Week 78 between bapineuzumab and placebo;
- Time to median placebo deterioration on ADAS-Cog/11 total score versus time to median bapineuzumab deterioration;
- Time to median placebo deterioration on DAD total score versus time to median bapineuzumab deterioration;
- Change from baseline to Week 78 in the total DS scores;
- Proportions of subjects with worsening from Baseline to Week 78 of at most 0, 3 and 7 points on the ADAS-Cog/11 total score;
- Proportions of subjects with worsening from Baseline to Week 78 of at most 0, 6, and 12 points on the DAD total score;
- ADAS-Cog/11 total score cumulative response curves (reverse cumulative distribution functions);
- DAD total score cumulative response curves (reverse cumulative distribution functions);
- Change from Baseline to Week 78 for the CDR-SOB total score.

Safety Evaluations: The evaluation of safety included incidence and severity of treatment-emergent adverse events (TEAEs) throughout the study and clinically important changes in safety assessment results including, as appropriate, vital signs, weight, clinical

laboratory tests, electrocardiograms (ECGs), clinical brain MRI scans, and physical and neurologic examinations.

Statistical Methods:

mITT Population: Defined as all randomized subjects who received at least 1 infusion or portion of an infusion of study drug and who had a Baseline and at least 1 Post-Baseline assessment of the ADAS-Cog/11 total score and DAD total score.

PIB PET Population: Included all randomized subjects who enrolled in the PET substudies and who met the following criteria: a) received at least 1 infusion or portion of an infusion of study drug, b) had a Baseline and at least 1 Post-Baseline PIB PET assessment, and c) had an SUVr for the global cortical average (GCA) ROI ≥1.35 at Baseline.

CSF Population: Included all randomized subjects who enrolled in the CSF substudies, received at least 1 infusion or portion of an infusion of study drug, and had a Baseline and at least 1 Post-Baseline CSF measurement (CSF p-tau).

vMRI Population: included all randomized subjects who enrolled in the vMRI substudies, received at least 1 infusion or portion of an infusion of study drug, and had a Baseline and at least 1 Post-Baseline vMRI that passed quality control and was satisfactory for volumetric analysis.

Safety Population: Included all randomized subjects who received at least 1 infusion or portion of an infusion of study drug. The analyses were performed according to the assigned treatment group and not actual treatment received. If some subjects received an inconsistent treatment or dose, these subjects were footnoted, or listed or summarized separately.

All PIB PET Subjects Population: Included all randomized subjects who enrolled in the PET substudies, received at least 1 infusion or portion of an infusion, and had a Baseline and at least 1 Post-Baseline PIB PET assessment, ie, subjects in the PIB PET population but without the requirement of a minimal degree of amyloid burden at Baseline. The analyses based on this population were performed by assigned treatment group and not actual treatment received.

Completer population: Defined as subjects in the mITT population who received at least 5 infusions, with 1 of the infusions being the Week 65 infusion, and who had Baseline and Week 78 assessments of the ADAS-Cog/11 total score and DAD total score. The analyses based on this population were performed according to the actual treatment received.

All study endpoints were summarized by treatment groups using descriptive statistics. The p-values refer to nominal (unadjusted) 2-sided p-values. Likewise, only nominal p-values and unadjusted confidence intervals (CIs) were presented in statistical tables.

The primary efficacy endpoints were analyzed using a restricted maximum likelihood (REML)-based mixed model for repeated-measures (MMRM). Analyses were conducted for the mITT population. The primary analysis was based on the treatment difference estimated at Week 78 using least squares (LS) means with factor levels weighted according to overall

baseline sample proportions. Both co-primary variables ADAS-Cog/11 total score and DAD total score had to reach statistical significance, ie, both p-values had to reach $p \leq 0.05$ in order to be declared effective.

Key secondary biomarker endpoints (PIB PET GCA SUVr and vMRI BBSI) were analyzed using the same MMRM as for the primary efficacy endpoints whereas an analysis of covariance (ANCOVA) model was applied to CSF p-tau.

RESULTS

Subject Disposition and Demography: Subject disposition and subjects analyzed for all randomized subjects is presented in Table 3. Of the 2212 subjects screened, 973 were screen failures and 140 had their eligibility withdrawn, resulting in 1099 randomized subjects (658 in the bapineuzumab group and 441 in the placebo group). The study was terminated early by the sponsor on 06 August 2012, when the results of 2 other Phase 3 trials of bapineuzumab showed no efficacy. Enrollment had already been completed at the time of decision to terminate. Subjects who were still participating at that time were asked to complete an early withdrawal visit.

Table 3. Subject Disposition and Subjects Analyzed - All Randomized Subjects

	Number (%) of Subjects	
	Placebo (N=441)	**Bapineuzumab (N=658)**
All randomized	441 (100)	658 (100)
Subjects received any amount of study treatment[a]	439 (99.5)	654 (99.4)
Subjects completed[b]	285 (64.6)	398 (60.5)
Subjects withdrawn[c]	155 (35.1)	256 (38.9)
Primary reason for withdrawal from treatment and/or study[d]		
Discontinuation of study by sponsor	65 (14.7)	88 (13.4)
Adverse event	34 (7.7)	60 (9.1)
Subject request	24 (5.4)	42 (6.4)
Other	11 (2.5)	20 (3.0)
Lost to follow-up	0	13 (2.0)
Investigator request	5 (1.1)	8 (1.2)
Protocol violation	4 (0.9)	8 (1.2)
Unsatisfactory response - efficacy	0	6 (0.9)
Death	4 (0.9)	4 (0.6)
Loss of caregiver	5 (1.1)	3 (0.5)
Vasogenic edema recurrence	1 (0.2)	3 (0.5)
Failed to return	2 (0.5)	1 (0.2)
Subject Populations for Analysis		
Safety	439 (99.5)	654 (99.4)
mITT	431 (97.7)	650 (98.8)
All PIB PET	24 (5.4)	33 (5.0)
PIB PET	24 (5.4)	32 (4.9)
CSF	62 (14.1)	76 (11.6)
vMRI	215 (48.8)	325 (49.4)
PK/PD	439 (99.5)	654 (99.4)
Completer	294 (66.7)	399 (60.6)

Denominators for percentages are the number of subjects randomized to treatment arms.
Reasons for withdrawal in decreasing order according to incidence in bapineuzumab group.
CSF = cerebrospinal fluid; mITT = modified intent-to-treat; N = number of subjects in population;
PD = pharmacodynamics; PIB PET = ^{11}C-Pittsburgh compound B positron emission tomography;
PK = pharmacokinetic; vMRI = volumetric magnetic resonance imaging.

a. Any amount of study treatment represents at least 1 infusion or portion of an infusion.
b. Subjects who did not terminate early from study treatment and completed the study up to and including Week 78. Subject participation status was unknown for 5 subjects (1 in placebo and 4 in bapineuzumab) due to missing conclusion of subject participation in study and/or conclusion of subject participation in treatment eCRF pages. Four of these subjects completed 6 infusions and the Week 78 visit. One subject completed 4 infusions and the Week 45 visit.
c. Subjects who terminated early from study treatment and/or study.
d. If subject discontinued from treatment and study, then reason for discontinuation from treatment was used for summary.

Demographic characteristics of subjects in the mITT population are presented in Table 4.

Table 4. Demographic Characteristics - mITT Population

	Placebo (N=431)	Bapineuzumab (N=650)	Total (N=1081)
Age (years), n	431 (100)	650 (100)	1081 (100)
Median (range)	70.0 (50-88)	71.5 (50-87)	71.0 (50-88)
Mean (SD)	70.2 (7.72)	70.9 (7.68)	70.7 (7.70)
Age category, n (%)			
<65 years	96 (22.3)	132 (20.3)	228 (21.1)
≥65 years	335 (77.7)	518 (79.7)	853 (78.9)
Sex, n (%)			
Male	172 (39.9)	231 (35.5)	403 (37.3)
Female	259 (60.1)	419 (64.5)	678 (62.7)
Race, n (%)			
Asian	69 (16.0)	115 (17.7)	184 (17.0)
Black or African American	3 (0.7)	5 (0.8)	8 (0.7)
White	356 (82.6)	517 (79.5)	873 (80.8)
Other	3 (0.7)	13 (2.0)	16 (1.5)
Height (cm), n	429 (99.5)	647 (99.5)	1076 (99.5)
Median (range)	163.00 (138.3-196.0)	162.50 (139.0-203.2)	162.60 (138.3-203.2)
Mean (SD)	163.88 (10.226)	163.31 (10.012)	163.54 (10.097)
Weight (kg), n	431 (100)	650 (100)	1081 (100)
Median (range)	67.100 (34.60-117.30)	66.350 (36.10-119.00)	67.000 (34.60-119.00)
Mean (SD)	68.138 (14.9483)	67.637 (15.3395)	67.837 (15.1797)

mITT = modified intent-to-treat; n = number of subjects with observation; N = number of subjects in population; SD = standard deviation.

Efficacy Results:

Change in ADAS-Cog/11 Total Score: ADAS-Cog/11 total scores (observed values and the change from Baseline at Week 78) in the mITT population are presented in Table 5. The LS mean change (standard error [SE]) from Baseline to Week 78 in the ADAS-Cog/11 total score was 7.32 (0.39) with bapineuzumab and 7.31 (0.47) with placebo. The difference between bapineuzumab and placebo (0.02) was not statistically significant (p=0.979).

Table 5. ADAS-Cog/11 Total Score: Observed Values and Change From Baseline at Week 78 (MMRM) - mITT Population

Time Point	Placebo (N=431)	Bapineuzumab (N=650)
Baseline		
n	431	650
Mean (SD)	22.6 (8.93)	23.2 (8.90)
Median (range)	21.0 (6, 53)	22.3 (4, 56)
Week 78		
n	300	414
Mean (SD)	28.0 (13.53)	28.8 (13.31)
Median (range)	24.8 (3, 68)	26.3 (3, 69)
Change from Baseline to Week 78		
n	300	414
Mean (SD)	6.2 (8.89)	6.4 (8.56)
Median (range)	4.5 (-11, 38)	5.3 (-11, 35)
MMRM analysis		
LS mean (SE)	7.31 (0.47)	7.32 (0.39)
Difference of LS means (95% CI)	-	0.02 (-1.18, 1.22)
p-Value	-	0.979

Results are from a restricted maximum likelihood -based MMRM with change from Baseline as the response and the following fixed effect model terms: treatment (bapineuzumab or placebo), visit (scheduled week), treatment-by-visit interaction, baseline value of the response variable, baseline-by-visit interaction, baseline mini-mental state examination total score stratum, baseline cholinesterase inhibitor and/or memantine use stratum, baseline age and apolipoprotein E ε4 allele copy number stratum.
Treatment differences were estimated using LS means with factor levels weighted according to overall population proportions.
ADAS-Cog/11 total score range is 0 (least impairment) to 70 (most impairment); a negative change from Baseline indicates a decrease in cognitive impairment.
ADAS-Cog/11 = Alzheimer's Disease Assessment Scale – Cognitive Subscale, 11-item total score;
CI = confidence interval; LS = least-squares; mITT = modified intent-to-treat; MMRM = mixed model for repeated measures; n = number of subjects in specified criteria; N = number of subjects in population;
SD = standard deviation; SE = standard error.

Change in DAD Total Score: DAD total scores (observed values and the change from Baseline at Week 78) in the mITT population are presented in Table 6. The LS mean change (SE) from Baseline to Week 78 in the DAD total score was -14.89 (0.84) with bapineuzumab and -14.94 (1.00) with placebo. The difference between bapineuzumab and placebo (0.04) was not statistically significant (p=0.973).

Table 6. DAD Total Score: Observed Values and Change From Baseline at Week 78 (MMRM) - mITT Population

Time Point	Placebo (N=431)	Bapineuzumab (N=650)
Baseline		
n	431	650
Mean (SD)	80.9 (18.66)	79.9 (18.26)
Median (range)	86.5 (13, 100)	85.0 (3, 100)
Week 78		
n	301	411
Mean (SD)	69.2 (24.47)	68.0 (24.85)
Median (range)	72.5 (3, 100)	71.8 (0, 100)
Change from Baseline to Week 78		
n	301	411
Mean (SD)	-13.0 (17.54)	-12.6 (18.31)
Median (range)	-8.1 (-80, 26)	-9.1 (-93, 36)
MMRM analysis		
LS mean (SE)	-14.94 (1.00)	-14.89 (0.84)
Difference of LS means (95% CI)		0.04 (-2.51, 2.60)
p-Value		0.973

Results are from a restricted maximum likelihood -based MMRM with change from Baseline as the response and the following fixed effect model terms: treatment (bapineuzumab or placebo), visit (scheduled week), treatment-by-visit interaction, baseline value of the response variable, baseline-by-visit interaction, baseline mini-mental state examination total score stratum, baseline cholinesterase inhibitor and/or memantine use stratum, baseline age and apolipoprotein E ε4 allele copy number stratum.
Treatment differences were estimated using LS means with factor levels weighted according to overall population proportions.
DAD total score range is 0 to 100, with higher scores indicating better function; a positive change from Baseline indicates an improvement.
CI = confidence interval; DAD = Disability Assessment for Dementia; LS = least-squares; mITT = modified intent-to-treat; MMRM = mixed model for repeated measures; n = number of subjects in specified criteria; N = number of subjects in population; SD = standard deviation; SE = standard error.

Change in PIB PET GCA SUVr: PIB PET GCA SUVr (observed values and the change from Baseline at Week 71) in the PIB PET population is presented in Table 7. The LS mean change (SE) from Baseline to Week 71 in the PIB PET GCA SUVr was -0.04 (0.03) with bapineuzumab and 0.03 (0.04) with placebo. The difference between bapineuzumab and placebo (-0.07) was not statistically significant (p=0.159).

Table 7. PIB PET GCA SUVr: Observed Values and Change From Baseline at Week 71 (MMRM) - PIB PET Population

Time Point	Placebo (N=24)	Bapineuzumab (N=32)
Baseline		
n	24	32
Mean (SD)	2.2 (0.29)	2.2 (0.31)
Median (range)	2.1 (1.7, 2.8)	2.2 (1.4, 2.9)
Week 71		
n	12	15
Mean (SD)	2.2 (0.32)	2.2 (0.32)
Median (range)	2.2 (1.6, 2.9)	2.2 (1.6, 2.9)
Change from Baseline to Week 71		
n	12	15
Mean (SD)	0.0 (0.16)	-0.0 (0.11)
Median (range)	0.0 (-0.3, 0.3)	-0.0 (-0.3, 0.2)
MMRM analysis		
LS mean (SE)	0.03 (0.04)	-0.04 (0.03)
Difference of LS means (95% CI)		-0.07 (-0.17, 0.03)
p-Value		0.159

Results are from a restricted maximum likelihood -based MMRM with change from Baseline as the response and the following fixed effect model terms: treatment (bapineuzumab or placebo), visit (scheduled week), treatment-by-visit interaction, baseline value of the response variable, baseline-by-visit interaction, baseline mini-mental state examination total score stratum, baseline cholinesterase inhibitor and/or memantine use stratum, baseline age and apolipoprotein E ε4 allele copy number stratum.
Treatment differences were estimated using LS means with factor levels weighted according to overall population proportions; a negative difference favors bapineuzumab.
CI = confidence interval; GCA = global cortical average; LS = least-squares; MMRM = mixed model for repeated measures; n = number of subjects in specified criteria; N = number of subjects in population; PIB = ^{11}C-Pittsburgh compound B; PET = positron emission tomography; SD = standard deviation; SE = standard error; SUVr = average standard uptake value ratio.

Change in CSF P-tau: CSF p-tau (observed values and the change from Baseline at Week 71) in the CSF population is presented in Table 8. The LS mean change (SE) from Baseline to Week 71 in the CSF p-tau was -0.55 (1.84) pg/mL with bapineuzumab and 0.83 (2.04) pg/mL with placebo (ANCOVA analysis; CSF population). The difference between bapineuzumab and placebo (-1.38) was not statistically significant (p=0.620).

Table 8. CSF p-tau: Observed Values and Change From Baseline at Week 71 (ANCOVA) - CSF Population

Time Point	Placebo (N=62)	Bapineuzumab (N=76)
Baseline		
n	62	76
Mean (SD) (pg/mL)	117.4 (40.67)	101.0 (38.95)
Median (range) (pg/mL)	111.4 (42, 241)	97.6 (43, 207)
Week 71		
n	62	76
Mean (SD) (pg/mL)	117.4 (41.35)	101.2 (37.60)
Median (range) (pg/mL)	112.7 (35, 228)	100.2 (39, 189)
Change from Baseline to Week 71		
n	62	76
Mean (SD) (pg/mL)	-0.0 (18.73)	0.2 (13.58)
Median (range) (pg/mL)	1.1 (-34, 79)	1.9 (-34, 57)
ANCOVA analysis		
LS mean (SE)	0.83 (2.04)	-0.55 (1.84)
Difference of LS means (95% CI)		-1.38 (-6.89, 4.13)
p-Value		0.620

Results are from an ANCOVA model with change from Baseline as the response variable and the following fixed effect model terms: treatment (bapineuzumab or placebo), baseline value of the response variable, mini-mental state examination total score stratum, cholinesterase inhibitor and/or memantine use stratum, baseline age and apolipoprotein E ε4 allele copy number stratum.
Treatment differences were estimated using LS means with factor levels weighted according to overall population proportions; a negative difference favors bapineuzumab.
ANCOVA = analysis of covariance; CI = confidence interval; CSF = cerebrospinal fluid; LS = least-squares; n = number of subjects in specified criteria; N = number of subjects in population; p-tau = phospho-tau; SD = standard deviation; SE = standard error.

Change in vMRI BBSI: vMRI BBSI (observed values and the change from Baseline at Week 71) in the vMRI population is presented in Table 9. The LS mean change (SE) from Baseline to Week 71 in the vMRI BBSI was 17.51 (0.56) mL with bapineuzumab and 17.64 (0.69) mL with placebo. The difference between bapineuzumab and placebo (-0.13) was not statistically significant (p=0.884).

Table 9. vMRI BBSI: Observed Values at Week 71 (MMRM) - vMRI Population

Time Point	Placebo (N=215)	Bapineuzumab (N=325)
Week 71		
n	131	197
Mean (SD) (mL)	17.1 (8.65)	17.4 (9.81)
Median (range) (mL)	16.9 (-0, 43)	16.5 (-1, 67)
MMRM analysis		
LS mean (SE) (mL)	17.64 (0.69)	17.51 (0.56)
Difference of LS means (95% CI) (mL)		-0.13 (-1.89, 1.63)
p-Value		0.884

Results are from a restricted maximum likelihood -based MMRM with change from Baseline as the response and the following fixed effect model terms: treatment (bapineuzumab or placebo), visit (scheduled week), treatment-by-visit interaction, baseline whole brain volume value of the response variable, baseline-by-visit interaction, baseline mini-mental state examination total score stratum, baseline cholinesterase inhibitor and/or memantine use stratum, baseline age and apolipoprotein E ε4 allele copy number stratum.
Treatment differences were estimated using LS means with factor levels weighted according to overall population proportions; a negative difference favors bapineuzumab.
BBSI = brain boundary shift integral; CI = confidence interval; LS = least-squares; MMRM = mixed model for repeated measures; n = number of subjects in specified criteria; N = number of subjects in population; SD = standard deviation; SE = standard error; vMRI = volumetric magnetic resonance imaging.

Divergence of Effect: The MMRM estimated slope (based on linear contrasts) of the differences between bapineuzumab and placebo for the ADAS-Cog/11 total scores and the DAD total scores from Week 39 to Week 78 was not statistically significant (mITT population) (Table 10).

Table 10. Divergence From Week 39 Through Week 78 in ADAS-Cog/11 Total Score and DAD Total Score - mITT Population

MMRM Estimate	Treatment Difference[a] Bapineuzumab 0.5 mg/kg - Placebo	
	ADAS-Cog/11 Total Score	DAD Total Score
Week 39	-0.27	-0.33
Week 52	-0.33	0.00
Week 65	-0.60	-0.91
Week 78	0.02	0.04
Estimates of slopes[b] (units/year) (SE)	0.24 (0.62)	0.09 (1.37)
95% CI	(-0.97, 1.45)	(-2.61, 2.78)
p-Value[c]	0.700	0.949

Positive divergence of effect is based on a statistically significant positive slope.
ADAS-Cog/11 = Alzheimer's Disease Assessment Scale – Cognitive Subscale; CI = confidence interval; DAD = Disability Assessment for Dementia: mITT = modified intent-to-treat; MMRM = mixed model for repeated measures; SE = standard error.

a. Results are from a restricted maximum likelihood-based MMRM with change from Baseline as the response and the following fixed effect model terms: treatment (bapineuzumab or placebo), visit (scheduled week), treatment-by-visit interaction, baseline value of the response variable, baseline-by-visit interaction, mini-mental state examination total score stratum, cholinesterase inhibitor and/or memantine use stratum, baseline age and apolipoprotein E ε4 allele copy number stratum.
b. Estimates are based on linear contrasts to estimate the slopes from Week 39 through Week 78 of the model estimated differences between the bapineuzumab dose group and placebo.
c. p-Value is testing the slope of a true treatment difference.

Deterioration on ADAS-Cog/11 Total Score (Time to Progression): The Kaplan Meier estimate of median time to first median placebo deterioration/time to first clinically meaningful deterioration in the mITT population showed no statistically significant difference in ADAS-Cog/11 total score between bapineuzumab and placebo according to the European Union (EU) definition (Table 11) and US definition (Table 12).

Table 11. Time (Days) to Median Placebo Deterioration in ADAS-Cog/11 Total Score - mITT Analysis Population

	Placebo (N=431)	Bapineuzumab 0.5 mg/kg (N=650)
Descriptive		
Number assessed, n (%)	431 (100)	650 (100)
Number censored, n (%)	199 (46.2)	303 (46.6)
Number of events, n (%)	232 (53.8)	347 (53.4)
Kaplan-meier estimates		
25th percentile (95% CI)	231.0 (187.0, 273.0)	268.0 (188.0, 274.0)
Median (95% CI)	463.0 (455.0, 546.0)	457.0 (455.0, 541.0)
75th percentile (95% CI)	NC (NC, NC)	NC (NC, NC)
Pairwise comparison:		
Bapineuzumab versus placebo[a]		
p-Value		0.684

Time to first median placebo deterioration was defined as the first time a subject experiences an increase (worsening) from Baseline in ADAS-Cog/11 greater than or equal to the median worsening observed at Week 78 in the placebo group. Denominators for percentages are the number of subjects assessed for treatment arms.
ADAS-Cog/11 = Alzheimer's Disease Assessment Scale – Cognitive Subscale; CI = confidence interval; mITT = modified intent-to-treat; n = number of subjects in specified criteria; N = number of subjects in population; NC = not computable.

a. Log rank test stratified by mini-mental state examination total score stratum, cholinesterase inhibitor and/or memantine use stratum, and number of copies of the apolipoprotein E ε4 allele was used to test whether there was a treatment difference between the bapineuzumab treated group and placebo group.

Table 12. Time (Days) to First Clinically Meaningful Deterioration in ADAS-Cog/11 Total Score - mITT Analysis Population

	Placebo (N=431)	Bapineuzumab 0.5 mg/kg (N=650)
Descriptive		
Number assessed, n (%)	431 (100)	650 (100)
Number censored, n (%)	261 (60.6)	389 (59.8)
Number of events, n (%)	170 (39.4)	261 (40.2)
Kaplan-meier estimates		
25th percentile (95% CI)	364.0 (281.0, 393.0)	363.0 (280.0, 365.0)
Median (95% CI)	NC (546.0, NC)	546.0 (546.0, NC)
75th percentile (95% CI)	NC (NC, NC)	NC (NC, NC)
Pairwise comparison:		
Bapineuzumab versus placebo[a]		
p-Value		0.383

Time to the first occurrence of a worsening on ADAS-Cog/11 total score of ≥7 points that is confirmed (ie, worsening ≥7 points) by the next nonmissing ADAS-Cog/11 assessment. .
ADAS-Cog/11 = Alzheimer's Disease Assessment Scale – Cognitive Subscale; CI = confidence interval; mITT = modified intent-to-treat; n = number of subjects in specified criteria; N = number of subjects in population; NC = not computable.

a. Log rank test stratified by mini-mental state examination total score stratum, cholinesterase inhibitor and/or memantine use stratum, and number of copies of the apolipoprotein E ε4 allele was used to test whether there was a treatment difference between the bapineuzumab treated group and placebo group.

Deterioration on DAD Total Score (Time to Progression): The Kaplan Meier estimate of median time to first median placebo deterioration/time to first clinically meaningful deterioration in the mITT population showed no statistically significant difference in DAD total score between bapineuzumab and placebo according to the EU definition (Table 13) and US definition (Table 14).

Table 13. Time (Days) to Median Placebo Deterioration in DAD Total Score - mITT Analysis Population

	Placebo (N=431)	Bapineuzumab 0.5 mg/kg (N=650)
Descriptive		
Number assessed, n (%)	431 (100)	650 (100)
Number censored, n (%)	198 (45.9)	301 (46.3)
Number of events, n (%)	233 (54.1)	349 (53.7)
Kaplan-meier estimates		
25th percentile (95% CI)	273.0 (190.0, 281.0)	189.0 (183.0, 269.0)
Median (95% CI)	464.0 (455.0, 546.0)	456.0 (449.0, 539.0)
75th percentile (95% CI)	NC (NC, NC)	NC (NC, NC)
Pairwise comparison:		
Bapineuzumab versus placebo[a]		
p-Value		0.191

Time to first median placebo deterioration was defined as the first time a subject experiences a decrease (worsening) in DAD from Baseline to Week 78 greater than or equal to the median worsening observed at Week 78 in the placebo group. Denominators for percentages are the number of subjects assessed for treatment arms.

CI = confidence interval; DAD = disability assessment for dementia; mITT = modified intent-to-treat; n = number of subjects in specified criteria; N = number of subjects in population; NC = not computable.

a. Log rank test stratified by mini-mental state examination total score stratum, cholinesterase inhibitor and/or memantine use stratum, and number of copies of the apolipoprotein E ε4 allele was used to test whether there was a treatment difference between the bapineuzumab treated group and placebo group.

Table 14. Time (Days) to First Clinically Meaningful Deterioration in DAD Total Score - mITT Analysis Population

	Placebo (N=431)	Bapineuzumab 0.5 mg/kg (N=650)
Descriptive		
Number assessed, n (%)	431 (100)	650 (100)
Number censored, n (%)	229 (53.1)	355 (54.6)
Number of events, n (%)	202 (46.9)	295 (45.4)
Kaplan-meier estimates		
25th percentile (95% CI)	358.0 (274.0, 365.0)	281.0 (273.0, 360.0)
Median (95% CI)	546.0 (542.0, 546.0)	546.0 (540.0, 546.0)
75th percentile (95% CI)	NC (NC, NC)	NC (NC, NC)
Pairwise comparison:		
Bapineuzumab versus placebo[a]		
p-Value		0.478

Time to first clinically meaningful deterioration was defined as the first time a subject experiences a decrease (worsening) from Baseline in DAD total score of 12 or greater. Denominators for percentages are the number of subjects assessed for treatment arms.
CI = confidence interval; DAD = disability assessment for dementia; mITT = modified intent-to-treat; n = number of subjects in specified criteria; N = number of subjects in population; NC = not computable.
a. Log rank test stratified by mini-mental state examination total score stratum, cholinesterase inhibitor and/or memantine use stratum, and number of copies of the apolipoprotein E ε4 allele is used to test whether there is a treatment difference between the bapineuzumab treated group and placebo group.

Change in DS Total Score: The LS mean change (SE) from Baseline to Week 78 in the DS total score was 1.22 (0.10) with bapineuzumab and 1.33 (0.12) with placebo (MMRM analysis; mITT population) (Table 15).

Table 15. Dependence Scale Total Score: Observed Values and Change From Baseline at Week 78 (MMRM) - mITT Analysis Population

Time Point	Placebo (N=431)	Bapineuzumab 0.5 mg/kg (N=650)
Baseline		
n	430	648
Mean (SD)	4.7 (2.17)	4.6 (2.32)
Median (range)	5.0 (0, 11)	5.0 (0, 13)
Week 78		
n	317	439
Mean (SD)	5.8 (2.67)	5.7 (2.78)
Median (range)	6.0 (0, 13)	6.0 (0, 14)
Change from Baseline to Week 78		
n	316	437
Mean (SD)	1.2 (2.21)	1.2 (2.32)
Median (range)	1.0 (-6, 9)	1.0 (-5, 11)
MMRM analysis		
LS mean (SE)	1.33 (0.12)	1.22 (0.10)
Difference of LS means (95% CI)		-0.11 (-0.41, 0.19)
p-Value		0.462

Results were from a restricted maximum likelihood-based MMRM with change from baseline as the response and the following fixed effect model terms: treatment (bapineuzumab or placebo), visit (scheduled week), treatment-by-visit interaction, baseline value of the response variable, baseline-by-visit interaction, baseline mini-mental state examination total score stratum, baseline cholinesterase inhibitor and/or memantine use stratum, baseline age and apolipoprotein E ε4 allele copy number stratum.
Treatment differences were estimated using LS means with factor levels weighted according to overall analysis population proportions. Dependence scale total score range is 0 to 15, with higher scores indicating worse impairment; a negative change from Baseline indicates an improvement.
CI = confidence interval; LS = least-squares; mITT = modified intent-to-treat; MMRM = mixed model for repeated measures; n = number of subjects in specified criteria; N = number of subjects in population; SD = standard deviation; SE = standard error.

Proportions of Subjects With Worsening From Baseline to Week 78 on ADAS-Cog/11 Total Score (mITT Population): In the EU analysis plan, the percentage of responders in the bapineuzumab and placebo groups was similar for each of the predefined limits for change in ADAS-Cog/11 total scores (Table 16). In the US analysis plan, the difference between the percentage of responders in the bapineuzumab and placebo groups was not statistically significant (Cochran-Mantel-Haenszel test) (Table 17).

Table 16. Proportions of Responders for ADAS-Cog/11 Total Score at Week 78 for EU - mITT Analysis Population

Worsening From Baseline to Week 78 in Total Score of Less Than or Equal to		Placebo (N=431)	Bapineuzumab 0.5 mg/kg (N=650)
0	n (%)	79 (18.3)	101 (15.5)
	(95% CI)	(14.8, 22.3)	(12.8, 18.6)
3	n (%)	131 (30.4)	166 (25.5)
	(95% CI)	(26.1, 35.0)	(22.2, 29.1)
7	n (%)	183 (42.5)	247 (38.0)
	(95% CI)	(37.7, 47.3)	(34.3, 41.9)

A responder was defined as a subject whose increase (worsening) from Baseline to Week 78 in ADAS-Cog/11 total score is (0, 3, 7) or less. Subjects who did not have a Week 78 value (because of early termination or missing data) were considered non-responders. Proportion was 100%∗(number of responders in the category)/N. The exact binominal 95% CI was calculated.
ADAS-Cog/11 = Alzheimer's Disease Assessment Scale – Cognitive Subscale; CI = confidence interval; EU = European Union; mITT = modified intent-to-treat; n = number of subjects in specified criteria; N = number of subjects in population.

Table 17. Responder Analysis for ADAS-Cog/11 Total Score at Week 78 for US (Cochran-Mantel-Haenszel test) - mITT Analysis Population

	Placebo (N=431)	Bapineuzumab 0.5 mg/kg (N=650)
Week 78		
Responder	182 (42.2)	241 (37.1)
p-Value[a]		0.086

A responder was defined as a subject whose increase (worsening) from Baseline to Week 78 in ADAS-Cog/11 total score was <7. Subjects who did not have a Week 78 value (because of early termination or missing data) were considered non-responders.
ADAS-Cog/11 = Alzheimer's Disease Assessment Scale – Cognitive Subscale; mITT = modified intent-to-treat; N = number of subjects in population; US = United States.
a. p-Value was from Cochran-Mantel-Haenszel test controlling for mini-mental state examination total score stratum and derived cholinesterase inhibitor and/or memantine use stratum.

Proportions of Subjects With Worsening From Baseline to Week 78 on DAD Total Score (mITT Population): In the EU analysis plan, the percentage of responders in the bapineuzumab and placebo groups was similar at each of the DAD total scores (Table 18). In the US analysis plan, the difference between the percentage of responders in the bapineuzumab and placebo groups was not statistically significant (Cochran-Mantel-Haenszel test) (Table 19).

Table 18. Proportions of Responders for DAD Total Score at Week 78 for EU - mITT Analysis Population

Worsening From Baseline to Week 78 in Total Score of Less Than or Equal to		Placebo (N=431)	Bapineuzumab 0.5 mg/kg (N=650)
0	n (%)	74 (17.2)	121 (18.6)
	(95% CI)	(13.7, 21.1)	(15.7, 21.8)
6	n (%)	129 (29.9)	178 (27.4)
	(95% CI)	(25.6, 34.5)	(24.0, 31.0)
12	n (%)	171 (39.7)	227 (34.9)
	(95% CI)	(35.0, 44.5)	(31.3, 38.7)

A responder was defined as a subject whose decrease (worsening) from Baseline to Week 78 in DAD total score was (0, 6, 12) or less. Subjects who did not have a Week 78 value (because of early termination or missing data) were considered non-responders. Proportion is 100%∗(number of responders in the category)/N. The exact binominal 95% CI was calculated.
CI = confidence interval; DAD = Disability Assessment for Dementia; EU = European Union; mITT = modified intent-to-treat; n = number of subjects in specified criteria; N = number of subjects in population.

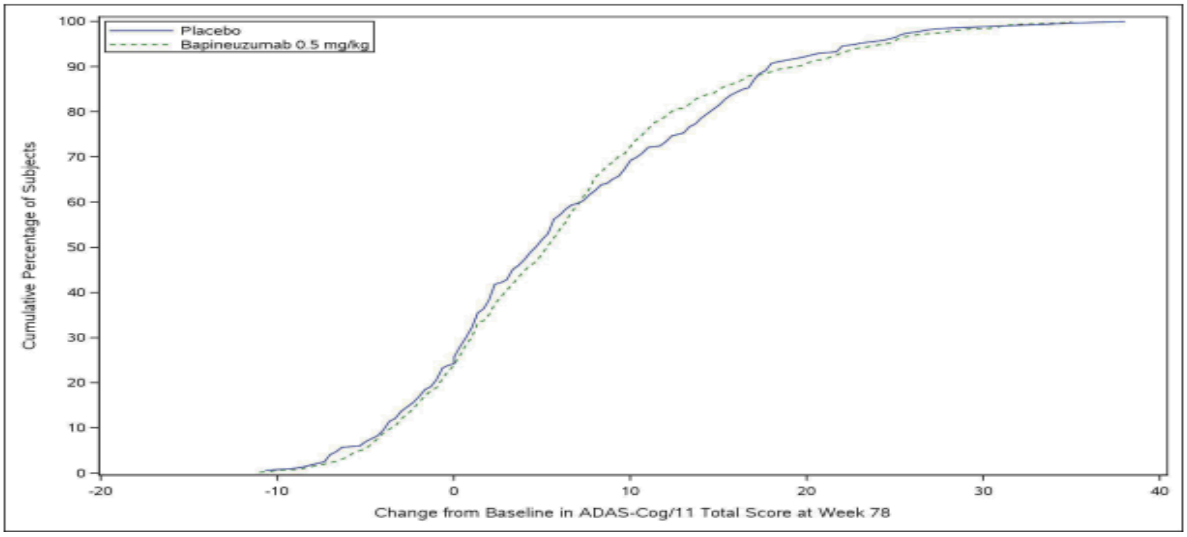
Table 19. Responder Analysis for DAD Total Score at Week 78 for US (Cochran-Mantel-Haenszel test) - mITT Analysis Population

	Placebo (N=431)	Bapineuzumab 0.5 mg/kg (N=650)
Week 78 Responder	171 (39.7)	227 (34.9)
p-Value[a]		0.120

A responder was defined as a subject whose decrease (worsening) from Baseline to Week 78 in DAD total score was <12. Subjects who did not have a Week 78 value (because of early termination or missing data) were considered non-responders.
DAD = Disability Assessment for Dementia; mITT = modified intent-to-treat; N = number of subjects in population; US = United States.
a. p-Value is from Cochran-Mantel-Haenszel (CMH) test controlling for MMSE total score stratum and derived cholinesterase inhibitor and/or memantine use stratum.

ADAS-Cog/11 Total Score Cumulative Response Curves at Week 78 (mITT population): Cumulative response curves at Week 78 for ADAS-Cog/11 total score in the mITT population are presented in Figure 1.

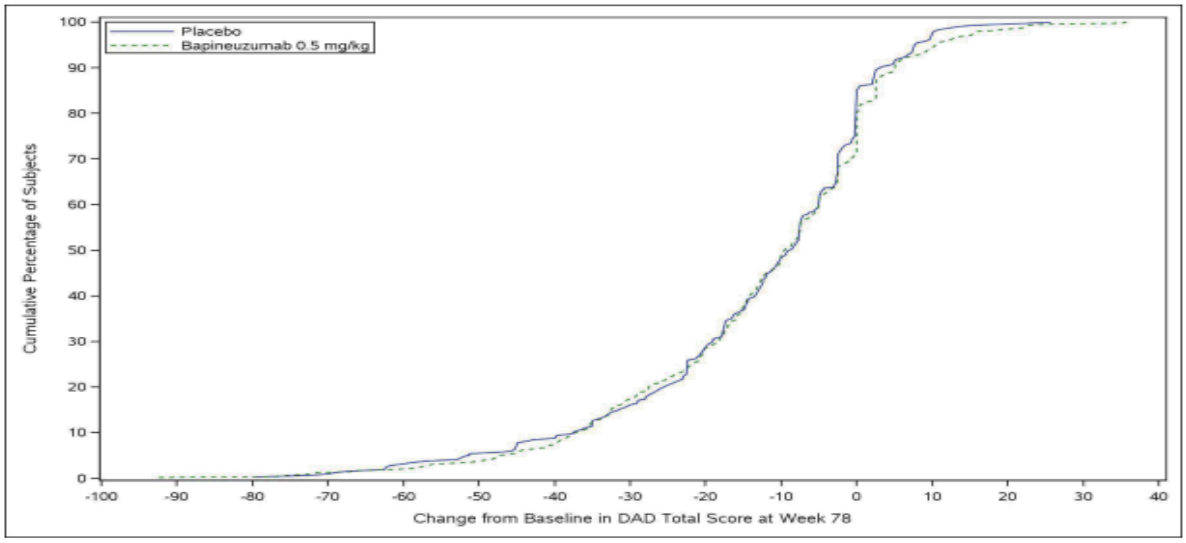
Figure 1. Cumulative Response Curves at Week 78 for ADAS-Cog/11 Total Score - mITT Analysis Population



Subjects without Week 78 assessment were not included in the analysis.
ADAS-Cog/11 = Alzheimer's Disease Assessment Scale – Cognitive Subscale; mITT = modified intent-to-treat.

DAD Total Score Cumulative Response Curves at Week 78 (mITT population): Cumulative response curves at Week 78 for DAD total score in the mITT population are presented in Figure 2.

Figure 2. Cumulative Response Curves at Week 78 for DAD Total Score - mITT Analysis Population



Subjects without Week 78 assessment were not included in the analysis.
DAD = Disability Assessment for Dementia; mITT = modified intent-to-treat.

Change From Baseline to Week 78 for CDR-SOB Total Score (mITT population): The LS mean change (SE) from Baseline to Week 78 in the CDR-SOB total score was 2.44 (0.13) with bapineuzumab and 2.59 (0.16) with placebo (Table 20).

Table 20. CDR-SOB Total Score: Observed Values and Change From Baseline at Week 78 (MMRM) - mITT Analysis Population

Time Point	Placebo (N=431)	Bapineuzumab 0.5 mg/kg (N=650)
Baseline		
n	430	650
Mean (SD)	5.1 (2.56)	5.3 (2.66)
Median (range)	4.5 (0, 15)	4.5 (1, 16)
Week 78		
n	311	427
Mean (SD)	7.3 (3.94)	7.4 (3.95)
Median (range)	7.0 (0, 18)	6.5 (1, 18)
Change from Baseline to Week 78		
n	310	427
Mean (SD)	2.4 (2.84)	2.3 (2.87)
Median (range)	2.0 (-4, 14)	1.5 (-6, 15)
MMRM analysis		
LS mean (SE)	2.59 (0.16)	2.44 (0.13)
Difference of LS means (95% CI)		-0.15 (-0.55, 0.24)
p-Value		0.448

Results were from a restricted maximum likelihood-based MMRM with change from Baseline as the response and the following fixed effect model terms: treatment (bapineuzumab or placebo), visit (scheduled week), treatment-by-visit interaction, baseline value of the response variable, baseline-by-visit interaction, baseline mini-mental state examination total score stratum, baseline cholinesterase inhibitor and/or memantine use stratum, baseline age and apolipoprotein E ε4 allele copy number stratum. Treatment differences were estimated using LS means with factor levels weighted according to overall analysis population proportions. CDR-SOB total score range is 0 (least impairment) to 18 (most impairment); a negative change from Baseline indicates an improvement.
CDR-SOB = Clinical Dementia Rating Sum of Boxes; CI = confidence interval; LS = least-squares; mITT = modified intent-to-treat; MMRM = mixed model for repeated measures; n = number of subjects in specified criteria; N = number of subjects in population; SD = standard deviation; SE = standard error.

Safety Results: An overview of adverse events (AEs) is presented in Table 21. The number of subjects with TEAEs was comparable between the 2 groups. Treatment-related TEAEs were reported in 34.6% of subjects in the bapineuzumab group and 22.1% in the placebo group (ie, a difference between groups of 12.5%). The treatment emergent serious adverse events (TESAEs) were reported by a numerically higher proportion of subjects in the bapineuzumab group than in the placebo group (20.9% versus [vs] 17.5% of subjects). This was also true for treatment related TESAEs (8.9% vs 2.3%). In addition, a numerically higher proportion of subjects discontinued from study due to treatment related TEAEs in the bapineuzumab group than in the placebo group (6.6% vs 2.3%). The proportion of subjects who died during the study was similar in the bapineuzumab and placebo groups (1.38% vs 1.82%).

Table 21. Overview of Adverse Events - Safety Population

Category	Number (%) of Subjects	
	Placebo (N=439)	Bapineuzumab (N=654)
AEs[a]	372 (84.7)	556 (85.0)
TEAEs[a]	365 (83.1)	551 (84.3)
TEAEs related to study drug[a]	97 (22.1)	226 (34.6)
SAEs	81 (18.5)	141 (21.6)
TESAEs	77 (17.5)	137 (20.9)
TESAEs related to study drug	10 (2.3)	58 (8.9)
Severe or life threatening AEs	59 (13.4)	88 (13.5)
Severe or life threatening TEAEs	54 (12.3)	83 (12.7)
Severe or life threatening TEAEs related to study drug	6 (1.4)	30 (4.6)
Discontinued due to AEs	36 (8.2)	65 (9.9)
Discontinued due to TEAEs	35 (8.0)	63 (9.6)
Discontinued due to TEAEs related to study drug	10 (2.3)	43 (6.6)
Dose reduced or temporary discontinuation due to AEs	18 (4.1)	99 (15.1)
Dose reduced or temporary discontinuation due to TEAEs	18 (4.1)	99 (15.1)
Dose reduced or temporary discontinuation due to TEAEs related to study drug	8 (1.8)	90 (13.8)
Deaths	8 (1.82)	9 (1.38)
Treatment emergent deaths	6 (1.37)	6 (0.92)

SAEs according to the Investigator's assessment.
Subjects discontinued were subjects withdrawn from study or discontinued treatment.
AE = adverse event; N = number of subjects in population; SAE = serious adverse event; TEAE = treatment emergent adverse event; TESAE = treatment emergent serious adverse event.
a. AE/SAE results are not separated out.

The incidence of TEAEs (all causalities) reported by ≥2% of subjects are presented in Table 22. The most common TEAEs (in >5% of subjects in either group) were vasogenic cerebral oedema, headache, cerebral microhemorrhage, nasopharyngitis, fall, depression, urinary tract infection, diarrhoea, anxiety, back pain, dizziness and hypertension. Cerebral microhemorrhage and vasogenic cerebral oedema were noticeably more common with bapineuzumab than placebo.

Table 22. Incidence of Treatment-Emergent Adverse Events (All Causalities) in ≥2% Subjects - Safety Analysis Population

Adverse Events by: System Organ Class and MedDRA Preferred Term	Number (%) of Subjects	
	Placebo (N=439)	Bapineuzumab (N=654)
Any treatment-emergent adverse event	365 (83.1)	551 (84.3)
Gastrointestinal disorders	105 (23.9)	131 (20.0)
Constipation	12 (2.7)	15 (2.3)
Diarrhoea	23 (5.2)	35 (5.4)
Gastrooesophageal reflux disease	9 (2.1)	6 (0.9)
Nausea	15 (3.4)	28 (4.3)
Vomiting	15 (3.4)	19 (2.9)
General disorders and administration site conditions	68 (15.5)	92 (14.1)
Fatigue	12 (2.7)	9 (1.4)
Irritability	3 (0.7)	17 (2.6)
Oedema peripheral	8 (1.8)	14 (2.1)
Infections and infestations	130 (29.6)	200 (30.6)
Bronchitis	15 (3.4)	13 (2.0)
Nasopharyngitis	34 (7.7)	45 (6.9)
Upper respiratory tract infection	10 (2.3)	23 (3.5)
Urinary tract infection	25 (5.7)	32 (4.9)
Injury, poisoning and procedural complications	95 (21.6)	123 (18.8)
Contusion	9 (2.1)	18 (2.8)
Fall	28 (6.4)	41 (6.3)
Laceration	10 (2.3)	12 (1.8)
Investigations	63 (14.4)	84 (12.8)
Weight decreased	10 (2.3)	21 (3.2)
Weight increased	16 (3.6)	8 (1.2)
Metabolism and nutrition disorders	31 (7.1)	50 (7.6)
Decreased appetite	7 (1.6)	13 (2.0)
Musculoskeletal and connective tissue disorders	76 (17.3)	123 (18.8)
Arthralgia	15 (3.4)	15 (2.3)
Back pain	16 (3.6)	33 (5.0)
Muscle spasms	10 (2.3)	10 (1.5)
Nervous system disorders	138 (31.4)	266 (40.7)
Cerebral microhaemorrhage	16 (3.6)	79 (12.1)
Dizziness	23 (5.2)	21 (3.2)
Headache	44 (10.0)	45 (6.9)
Syncope	6 (1.4)	14 (2.1)
Vasogenic cerebral oedema	9 (2.1)	109 (16.7)
Psychiatric disorders	105 (23.9)	130 (19.9)
Agitation	14 (3.2)	28 (4.3)
Anxiety	26 (5.9)	30 (4.6)
Confusional state	12 (2.7)	15 (2.3)
Depression	27 (6.2)	35 (5.4)
Insomnia	14 (3.2)	16 (2.4)
Respiratory, thoracic and mediastinal disorders	37 (8.4)	45 (6.9)
Cough	13 (3.0)	16 (2.4)
Skin and subcutaneous tissue disorders	52 (11.8)	65 (9.9)
Rash	9 (2.1)	14 (2.1)
Vascular disorders	37 (8.4)	59 (9.0)
Hypertension	22 (5.0)	18 (2.8)

Table 22. Incidence of Treatment-Emergent Adverse Events (All Causalities) in ≥2% Subjects - Safety Analysis Population

AE/SAE results are not separated out. Denominators for percentages are the number of subjects in the safety population. Subjects were counted only once per treatment in each row. MedDRA (version 15.0) coding dictionary applied.
AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects in population; SAE = serious adverse event.

Treatment related TEAEs reported by ≥2% of subjects are presented in Table 23. The most common treatment related TEAEs were vasogenic cerebral oedema (16.5% of subjects with bapineuzumab vs 2.1% of subjects with placebo), cerebral microhemorrhage (10.7% vs 2.5%) and headache (3.2% vs 3.4%). Treatment related cerebral microhemorrhage and vasogenic cerebral oedema were noticeably more common with bapineuzumab than placebo.

Table 23. Incidence of Treatment-Emergent Adverse Events (Treatment Related) in ≥2% Subjects - Safety Analysis Population

Adverse Events by: System Organ Class and MedDRA Preferred Term	Number (%) of Subjects	
	Placebo (N=439)	Bapineuzumab (N=654)
Any treatment-emergent adverse event	97 (22.1)	226 (34.6)
Nervous system disorders	56 (12.8)	172 (26.3)
Cerebral microhaemorrhage	11 (2.5)	70 (10.7)
Headache	15 (3.4)	21 (3.2)
Vasogenic cerebral oedema	9 (2.1)	108 (16.5)

AE/SAE results are not separated out. MedDRA (version 15.0) coding dictionary applied.
AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects in population; SAE = serious adverse event.

Serious Adverse Events: The incidence of TESAEs (all causalities) are presented in Table 24. The most common TESAEs were vasogenic cerebral oedema (6.1% of subjects with bapineuzumab vs 0.9% of subjects with placebo), pneumonia (0.9% vs 0.7), and deep vein thrombosis (0.8% vs 0.2%). Vasogenic cerebral oedema was more commonly reported with bapineuzumab than placebo.

Table 24. Incidence of Treatment-Emergent Serious Adverse Events (All Causalities) - Safety Analysis Population

Adverse Events by: System Organ Class and MedDRA Preferred Term	Number (%) of Subjects	
	Placebo (N=439)	Bapineuzumab (N=654)
Any treatment-emergent serious adverse event	77 (17.5)	137 (20.9)
Blood and lymphatic system disorders	2 (0.5)	1 (0.2)
Anaemia	1 (0.2)	0
Bone marrow failure	0	1 (0.2)
Leukocytosis	1 (0.2)	0
Cardiac disorders	10 (2.3)	10 (1.5)
Acute myocardial infarction	1 (0.2)	0
Angina pectoris	2 (0.5)	1 (0.2)
Angina unstable	0	1 (0.2)
Atrial fibrillation	0	1 (0.2)
Atrioventricular block complete	0	2 (0.3)
Atrioventricular block second degree	0	1 (0.2)
Bradycardia	1 (0.2)	1 (0.2)
Cardiac arrest	1 (0.2)	1 (0.2)
Cardiovascular insufficiency	1 (0.2)	0
Hypertensive heart disease	1 (0.2)	0
Myocardial infarction	1 (0.2)	0
Myocardial ischaemia	0	1 (0.2)
Sinus bradycardia	1 (0.2)	0
Supraventricular tachycardia	1 (0.2)	1 (0.2)
Tachycardia	1 (0.2)	0
Eye disorders	0	2 (0.3)
Cataract	0	2 (0.3)
Vitreous haemorrhage	0	1 (0.2)
Gastrointestinal disorders	7 (1.6)	12 (1.8)
Abdominal pain	1 (0.2)	1 (0.2)
Abdominal pain upper	0	1 (0.2)
Anal haemorrhage	0	1 (0.2)
Colonic polyp	1 (0.2)	0
Diarrhoea	0	1 (0.2)
Duodenal ulcer perforation	0	1 (0.2)
Gastric ulcer	0	1 (0.2)
Gastrointestinal ulcer haemorrhage	0	1 (0.2)
Haematemesis	1 (0.2)	0
Ileus	0	1 (0.2)
Inguinal hernia	2 (0.5)	0
Inguinal hernia, obstructive	1 (0.2)	0
Intestinal obstruction	1 (0.2)	0
Nausea	0	2 (0.3)
Oesophageal ulcer	0	1 (0.2)
Pancreatitis	0	1 (0.2)
Pancreatitis acute	0	1 (0.2)
Vomiting	0	1 (0.2)
General disorders and administration site conditions	5 (1.1)	7 (1.1)
Chest discomfort	1 (0.2)	0
Chest pain	1 (0.2)	2 (0.3)
Device occlusion	0	1 (0.2)
Fibrosis	0	1 (0.2)
General physical health deterioration	0	1 (0.2)

Table 24. Incidence of Treatment-Emergent Serious Adverse Events (All Causalities) - Safety Analysis Population

Adverse Events by: System Organ Class and MedDRA Preferred Term	Number (%) of Subjects	
	Placebo (N=439)	Bapineuzumab (N=654)
Malaise	1 (0.2)	0
Non-cardiac chest pain	1 (0.2)	0
Pain	1 (0.2)	0
Pyrexia	0	2 (0.3)
Hepatobiliary disorders	2 (0.5)	4 (0.6)
Bile duct stone	1 (0.2)	0
Cholangitis	0	1 (0.2)
Cholecystitis	1 (0.2)	1 (0.2)
Cholelithiasis	0	1 (0.2)
Gallbladder disorder	0	1 (0.2)
Hepatic function abnormal	0	1 (0.2)
Jaundice	0	1 (0.2)
Immune system disorders	0	1 (0.2)
Hypersensitivity	0	1 (0.2)
Infections and infestations	14 (3.2)	18 (2.8)
Abdominal abscess	0	1 (0.2)
Abscess	0	1 (0.2)
Appendicitis	0	2 (0.3)
Bacterial sepsis	0	1 (0.2)
Bronchitis	0	1 (0.2)
Cellulitis	0	1 (0.2)
Gastroenteritis	1 (0.2)	1 (0.2)
Herpes zoster	1 (0.2)	0
Infected skin ulcer	1 (0.2)	0
Kidney infection	0	1 (0.2)
Lower respiratory tract infection	1 (0.2)	0
Meningitis cryptococcal	1 (0.2)	0
Osteomyelitis	0	1 (0.2)
Paronychia	1 (0.2)	0
Pneumonia	3 (0.7)	6 (0.9)
Pseudomembranous colitis	1 (0.2)	0
Pyelonephritis	1 (0.2)	0
Sepsis	3 (0.7)	1 (0.2)
Toxic shock syndrome	0	1 (0.2)
Urinary tract infection	2 (0.5)	2 (0.3)
Urosepsis	0	1 (0.2)
Vaginitis bacterial	1 (0.2)	0
Viral upper respiratory tract infection	1 (0.2)	0
Injury, poisoning and procedural complications	12 (2.7)	16 (2.4)
Accidental overdose	1 (0.2)	2 (0.3)
Ankle fracture	0	1 (0.2)
Contusion	1 (0.2)	0
Drug administration error	0	1 (0.2)
Excoriation	0	1 (0.2)
Eye injury	0	1 (0.2)
Fall	1 (0.2)	2 (0.3)
Femoral neck fracture	0	2 (0.3)
Femur fracture	1 (0.2)	3 (0.5)
Head injury	0	1 (0.2)

Table 24. Incidence of Treatment-Emergent Serious Adverse Events (All Causalities) - Safety Analysis Population

Adverse Events by: System Organ Class and MedDRA Preferred Term	Number (%) of Subjects	
	Placebo (N=439)	Bapineuzumab (N=654)
Hip fracture	2 (0.5)	1 (0.2)
Humerus fracture	0	1 (0.2)
Post lumbar puncture syndrome	1 (0.2)	0
Pubis fracture	0	1 (0.2)
Radius fracture	2 (0.5)	0
Rib fracture	1 (0.2)	0
Spinal compression fracture	2 (0.5)	1 (0.2)
Stab wound	1 (0.2)	0
Subdural haematoma	1 (0.2)	0
Upper limb fracture	1 (0.2)	0
Wrist fracture	2 (0.5)	0
Investigations	2 (0.5)	1 (0.2)
Blood pressure increased	1 (0.2)	0
Fibrin D dimer increased	1 (0.2)	0
Heart rate increased	1 (0.2)	0
Streptococcus test positive	0	1 (0.2)
Metabolism and nutrition disorders	3 (0.7)	4 (0.6)
Dehydration	2 (0.5)	3 (0.5)
Hypoglycaemia	1 (0.2)	0
Hypokalaemia	0	1 (0.2)
Hyponatraemia	0	2 (0.3)
Musculoskeletal and connective tissue disorders	6 (1.4)	9 (1.4)
Arthralgia	1 (0.2)	0
Arthritis	0	1 (0.2)
Back pain	1 (0.2)	2 (0.3)
Intervertebral disc protrusion	0	1 (0.2)
Lumbar spinal stenosis	0	1 (0.2)
Osteoarthritis	1 (0.2)	1 (0.2)
Polymyalgia rheumatica	0	1 (0.2)
Rhabdomyolysis	2 (0.5)	2 (0.3)
Spinal column stenosis	1 (0.2)	0
Neoplasms benign, malignant and unspecified (including cysts and polyps)	14 (3.2)	8 (1.2)
Adenocarcinoma	0	1 (0.2)
Basal cell carcinoma	0	1 (0.2)
Bladder cancer	1 (0.2)	0
Breast cancer	2 (0.5)	2 (0.3)
Breast neoplasm	1 (0.2)	0
Hepatic neoplasm	1 (0.2)	0
Leiomyosarcoma	0	1 (0.2)
Lentigo maligna	0	1 (0.2)
Metastatic neoplasm	0	1 (0.2)
Neoplasm prostate	1 (0.2)	0
Oesophageal carcinoma	1 (0.2)	0
Prostate cancer	4 (0.9)	1 (0.2)
Squamous cell carcinoma	3 (0.7)	0
Nervous system disorders	12 (2.7)	63 (9.6)
Amyotrophic lateral sclerosis	0	1 (0.2)
Aphasia	0	1 (0.2)

Table 24. Incidence of Treatment-Emergent Serious Adverse Events (All Causalities) - Safety Analysis Population

Adverse Events by: System Organ Class and MedDRA Preferred Term	Number (%) of Subjects	
	Placebo (N=439)	Bapineuzumab (N=654)
Brain stem ischaemia	1 (0.2)	0
Cerebral haemorrhage	1 (0.2)	3 (0.5)
Cerebral haemosiderin deposition	1 (0.2)	0
Cerebral infarction	1 (0.2)	0
Cerebral ischaemia	0	1 (0.2)
Cerebral microhaemorrhage	0	4 (0.6)
Cerebrovascular accident	1 (0.2)	0
Convulsion	0	3 (0.5)
Dizziness	0	1 (0.2)
Epilepsy	0	1 (0.2)
Grand mal convulsion	1 (0.2)	2 (0.3)
Haemorrhagic stroke	1 (0.2)	0
Hydrocephalus	0	1 (0.2)
Ischaemic stroke	0	2 (0.3)
Lacunar infarction	1 (0.2)	0
Lethargy	0	1 (0.2)
Loss of consciousness	0	1 (0.2)
Mental impairment	0	1 (0.2)
Paraesthesia	0	1 (0.2)
Presyncope	0	1 (0.2)
Syncope	2 (0.5)	4 (0.6)
Transient ischaemic attack	0	1 (0.2)
Vasogenic cerebral oedema	4 (0.9)	40 (6.1)
Visual field defect	0	1 (0.2)
Psychiatric disorders	10 (2.3)	10 (1.5)
Abnormal behaviour	1 (0.2)	0
Aggression	1 (0.2)	0
Agitation	1 (0.2)	2 (0.3)
Completed suicide	0	1 (0.2)
Confusional state	2 (0.5)	3 (0.5)
Delirium	1 (0.2)	2 (0.3)
Depression	1 (0.2)	0
Hallucination	1 (0.2)	1 (0.2)
Mental status changes	2 (0.5)	3 (0.5)
Restlessness	1 (0.2)	0
Suicide attempt	1 (0.2)	0
Renal and urinary disorders	1 (0.2)	5 (0.8)
Acute prerenal failure	0	1 (0.2)
Haematuria	0	1 (0.2)
Pollakiuria	0	1 (0.2)
Renal failure acute	1 (0.2)	2 (0.3)
Reproductive system and breast disorders	2 (0.5)	2 (0.3)
Benign prostatic hyperplasia	0	1 (0.2)
Breast mass	1 (0.2)	1 (0.2)
Rectocele	1 (0.2)	0
Respiratory, thoracic and mediastinal disorders	6 (1.4)	5 (0.8)
Asthma	0	1 (0.2)
Paranasal cyst	1 (0.2)	0
Pneumonia aspiration	1 (0.2)	1 (0.2)

Table 24. Incidence of Treatment-Emergent Serious Adverse Events (All Causalities) - Safety Analysis Population

Adverse Events by: System Organ Class and MedDRA Preferred Term	Number (%) of Subjects	
	Placebo (N=439)	Bapineuzumab (N=654)
Pulmonary embolism	2 (0.5)	3 (0.5)
Pulmonary oedema	1 (0.2)	0
Respiratory failure	1 (0.2)	0
Social circumstances	0	1 (0.2)
Social problem	0	1 (0.2)
Surgical and medical procedures	0	1 (0.2)
Thyroidectomy	0	1 (0.2)
Uncoded	0	1 (0.2)
Uncoded	0	1 (0.2)
Vascular disorders	2 (0.5)	7 (1.1)
Arteriosclerosis	1 (0.2)	0
Deep vein thrombosis	1 (0.2)	5 (0.8)
Ischaemia	0	1 (0.2)
Peripheral artery stenosis	0	1 (0.2)

MedDRA (version 15.0) coding dictionary applied.
MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects in population.

Treatment related TESAEs are presented in Table 25. TESAEs related to treatment were reported in 58 (8.9%) subjects in the bapineuzumab group and 10 (2.3%) subjects in the placebo group. The most common TESAEs related to treatment were vasogenic cerebral oedema (40 [6.1%] subjects with bapineuzumab vs 4 [0.9%] subjects with placebo), cerebral haemorrhage (3 [0.5%] vs 1[0.2%]), cerebral microhemorrhage (4 [0.6%] vs 0), pulmonary embolism (2 [0.3%] vs 0) and deep vein thrombosis (2 [0.3%] vs 0).

Table 25. Incidence of Treatment-Emergent Serious Adverse Events (Treatment-Related) - Safety Analysis Population

Adverse Events by: System Organ Class and MedDRA Preferred Term	Number (%) of Subjects	
	Placebo (N=439)	Bapineuzumab (N=654)
Any treatment-emergent serious adverse event	10 (2.3)	58 (8.9)
Blood and lymphatic system disorders	0	1 (0.2)
Bone marrow failure	0	1 (0.2)
Cardiac disorders	1 (0.2)	2 (0.3)
Atrial fibrillation	0	1 (0.2)
Cardiac arrest	0	1 (0.2)
Myocardial infarction	1 (0.2)	0
Gastrointestinal disorders	0	1 (0.2)
Duodenal ulcer perforation	0	1 (0.2)
Hepatobiliary disorders	0	1 (0.2)
Jaundice	0	1 (0.2)
Immune system disorders	0	1 (0.2)
Hypersensitivity	0	1 (0.2)
Infections and infestations	0	1 (0.2)
Pneumonia	0	1 (0.2)
Injury, poisoning and procedural complications	1 (0.2)	0
Subdural haematoma	1 (0.2)	0
Nervous system disorders	9 (2.1)	46 (7.0)
Brain stem ischaemia	1 (0.2)	0
Cerebral haemorrhage	1 (0.2)	3 (0.5)
Cerebral haemosiderin deposition	1 (0.2)	0
Cerebral microhaemorrhage	0	4 (0.6)
Cerebrovascular accident	1 (0.2)	0
Convulsion	0	1 (0.2)
Grand mal convulsion	1 (0.2)	1 (0.2)
Haemorrhagic stroke	1 (0.2)	0
Hydrocephalus	0	1 (0.2)
Ischaemic stroke	0	1 (0.2)
Lacunar infarction	1 (0.2)	0
Vasogenic cerebral oedema	4 (0.9)	40 (6.1)
Psychiatric disorders	1 (0.2)	1 (0.2)
Delirium	1 (0.2)	1 (0.2)
Respiratory, thoracic and mediastinal disorders	0	3 (0.5)
Pneumonia aspiration	0	1 (0.2)
Pulmonary embolism	0	2 (0.3)
Vascular disorders	0	2 (0.3)
Deep vein thrombosis	0	2 (0.3)

MedDRA (version 15.0) coding dictionary applied.
MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects in population.

Deaths: A total of 17 subjects died overall: 9 in the bapineuzumab group and 8 in the placebo group. Of these deaths, 5 were not treatment emergent: 3 in the bapineuzumab group (due to lung neoplasm malignant, intestinal ischaemia and acute coronary syndrome) and 2 in the placebo group (due to pneumonia aspiration and cerebral infarction).

A total of 12 deaths were due to TEAEs: 6 in the bapineuzumab group (due to toxic shock syndrome; metastatic neoplasm; excoriation, streptococcus test positive and mental status changes; completed suicide; amyotrophic lateral sclerosis; and bone marrow failure) and 6 in

the placebo group (due to hepatic neoplasm; oesophageal carcinoma; cardiovascular insufficiency and respiratory failure; cardiac arrest; hypertensive heart disease; and arteriosclerosis and hemorrhagic stroke).

Of the 12 deaths due to TEAEs, 2 were due to TEAEs that were assessed by the Investigator as related to treatment (1 subject in the bapineuzumab [bone marrow failure] and 1 subject in the placebo group [hemorrhagic stroke]).

TEAEs causing permanent discontinuation from treatment or study are presented in Table 26.

Table 26. Treatment-Emergent Adverse Events That Caused Discontinuation From Treatment or Study (All Causalities) - Safety Analysis Population

Adverse Events by: System Organ Class and MedDRA Preferred Term	Number (%) of Subjects	
	Placebo (N=439)	Bapineuzumab (N=654)
Any treatment-emergent adverse event that caused discontinuation from treatment or study	35 (8.0)	63 (9.6)
Blood and lymphatic system disorders	0	2 (0.3)
Bone marrow failure	0	1 (0.2)
Thrombocytopenia	0	1 (0.2)
Cardiac disorders	3 (0.7)	2 (0.3)
Atrial fibrillation	0	1 (0.2)
Atrioventricular block complete	0	1 (0.2)
Cardiovascular insufficiency	1 (0.2)	0
Myocardial infarction	1 (0.2)	0
Sinus bradycardia	1 (0.2)	0
Gastrointestinal disorders	0	1 (0.2)
Epigastric discomfort	0	1 (0.2)
General disorders and administration site conditions	1 (0.2)	2 (0.3)
Disuse syndrome	0	1 (0.2)
Fatigue	0	1 (0.2)
Pain	1 (0.2)	0
Hepatobiliary disorders	0	1 (0.2)
Jaundice	0	1 (0.2)
Immune system disorders	0	1 (0.2)
Hypersensitivity	0	1 (0.2)
Infections and infestations	2 (0.5)	0
Infected skin ulcer	1 (0.2)	0
Meningitis cryptococcal	1 (0.2)	0
Sepsis	1 (0.2)	0
Injury, poisoning and procedural complications	2 (0.5)	1 (0.2)
Subdural haematoma	2 (0.5)	1 (0.2)
Musculoskeletal and connective tissue disorders	1 (0.2)	0
Osteoporosis	1 (0.2)	0
Neoplasms benign, malignant and unspecified (including cysts and polyps)	7 (1.6)	8 (1.2)
Adenocarcinoma	0	1 (0.2)
Bladder cancer	1 (0.2)	0
Breast cancer	1 (0.2)	2 (0.3)
Breast neoplasm	1 (0.2)	0
Essential thrombocythaemia	0	1 (0.2)
Leiomyosarcoma	0	1 (0.2)
Metastatic neoplasm	0	1 (0.2)
Oesophageal carcinoma	1 (0.2)	0
Prostate cancer	3 (0.7)	2 (0.3)
Nervous system disorders	12 (2.7)	36 (5.5)
Carotid artery aneurysm	1 (0.2)	0
Cerebral haemorrhage	0	3 (0.5)
Cerebral haemosiderin deposition	2 (0.5)	2 (0.3)
Cerebral infarction	1 (0.2)	2 (0.3)
Cerebral microhaemorrhage	1 (0.2)	4 (0.6)
Cerebrovascular accident	1 (0.2)	0
Cognitive disorder	0	1 (0.2)
Convulsion	0	1 (0.2)

Table 26. Treatment-Emergent Adverse Events That Caused Discontinuation From Treatment or Study (All Causalities) - Safety Analysis Population

Adverse Events by: System Organ Class and MedDRA Preferred Term	Number (%) of Subjects	
	Placebo (N=439)	Bapineuzumab (N=654)
Dementia	1 (0.2)	0
Grand mal convulsion	0	2 (0.3)
Haemorrhagic stroke	1 (0.2)	0
Ischaemic stroke	0	1 (0.2)
Lacunar infarction	1 (0.2)	1 (0.2)
Mental impairment	0	1 (0.2)
Migraine	0	1 (0.2)
Syncope	1 (0.2)	0
Vasogenic cerebral oedema	2 (0.5)	19 (2.9)
Psychiatric disorders	3 (0.7)	4 (0.6)
Aggression	0	1 (0.2)
Agitation	1 (0.2)	1 (0.2)
Anxiety	1 (0.2)	0
Completed suicide	0	1 (0.2)
Confusional state	0	1 (0.2)
Delirium	0	1 (0.2)
Hallucination	0	1 (0.2)
Restlessness	1 (0.2)	0
Respiratory, thoracic and mediastinal disorders	3 (0.7)	2 (0.3)
Pneumonia aspiration	1 (0.2)	0
Pulmonary embolism	1 (0.2)	2 (0.3)
Respiratory failure	1 (0.2)	0
Skin and subcutaneous tissue disorders	1 (0.2)	1 (0.2)
Rash maculo-papular	1 (0.2)	0
Urticaria	0	1 (0.2)
Vascular disorders	1 (0.2)	3 (0.5)
Deep vein thrombosis	0	3 (0.5)
Vein disorder	1 (0.2)	0

Denominators for percentages are the number of subjects in the safety population.
Subjects are counted only once per treatment in each row.
MedDRA (version 15.0) coding dictionary applied.
MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects in population.

No clinically relevant abnormal trends in vital signs or ECGs results were noted.

CONCLUSIONS: The study did not prove the primary hypothesis. The difference between IV bapineuzumab 0.5 mg/kg and placebo was not statistically significant for change from Baseline in either ADAS/Cog-11 or DAD total scores at Week 78. The LS mean change (SE) from Baseline to Week 78 in the ADAS-Cog/11 total score was 7.32 (0.39) with IV bapineuzumab 0.5 mg/kg and 7.31 (0.47) with placebo (MMRM analysis). The LS mean change (SE) from Baseline to Week 78 in the DAD total score was -14.89 (0.84) with IV bapineuzumab 0.5 mg/kg and -14.94 (1.00) with placebo (MMRM analysis). Both of these results show that both groups worsened to a similar extent over the 78 weeks of the study.

Infusions of bapineuzumab 0.5 mg/kg every 13 weeks were generally well tolerated, with a safety and tolerability profile that was similar to that observed in previous studies. The incidence of VE reported in the bapineuzumab group was consistent with previous studies.

This is a conclusively negative study. Although the study was terminated early, the available clinical data (ADAS-Cog and DAD) were consistent with data from previous studies. In addition, findings were consistent with observational data from the literature suggesting that the study was not a failed trial. Clinical findings, including clinical endpoints, biomarker endpoints, and safety/tolerability, observed in this study are generally consistent with those of previously completed studies.