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GENERIC DRUG NAME / COMPOUND NUMBER: Bapineuzumab / PF-05236801

PROTOCOL NO.: 3133K1-3003 (B2521004)

PROTOCOL TITLE: Phase 3 Extension, Multicenter, Double-Blind, Parallel-Group, Long-term Safety and Tolerability Trials of Bapineuzumab (AAB-001, ELN115727) in Subjects With Alzheimer Disease Who Are Apolipoprotein E ε4 Carriers and Participated in Study 3133K1-3001-WW or Study 3133K1-3001-US

Study Centers: A total of 147 centers took part in the study and enrolled subjects; 1 in Argentina, 6 in Australia, 5 in Belgium, 1 in Chile, 2 in Finland, 18 in France, 4 in Italy, 29 in Japan, 4 in Netherlands, 2 in New Zealand, 4 in Poland, 3 in Portugal, 2 in Slovakia, 2 in South Africa, 11 in Spain, 2 in Sweden, 1 in Switzerland, 9 in the United Kingdom , 41 in the United States.

Study Initiation and Final Completion Dates: 11 Dec 2009 to 16 Oct 2012
The study was terminated prematurely on 06 August 2012.

Phase of Development: Phase 3

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

Study Objectives:

Primary Objective: The primary objective of this study was to evaluate the long-term safety and tolerability of intravenously (IV)-administered bapineuzumab in subjects with Alzheimer's disease (AD).

METHODS

Study Design: This was a Phase 3, multicenter, randomized, double-blind, long-term extension study to a previous base study, (A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Efficacy and Safety Trial of Bapineuzumab in Subjects With Mild to Moderate Alzheimer Disease Who Are Apolipoprotein E ε4 Carriers [NCT00676143]). This study was designed to investigate the long-term safety, tolerability, and exploratory measures of efficacy, biomarkers, health outcomes, immunogenicity, and biochemical characterization of bapineuzumab administered IV every 13 weeks in subjects with AD who were ApoE4 carriers over 4 years (208 weeks). Whether or not they had been assigned to active treatment or placebo in the previous base study, all subjects received 0.5 mg/kg bapineuzumab via IV infusion once every 13 weeks in this study.

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 recently completed bapineuzumab IV Phase 3 studies; therefore, this study was terminated earlier than planned.

The schedule of study activities is summarized in Table 1, Table 2 and Table 3.

Table 1. Study Flowchart – 1st Year

First Year, Study Week (W)	Screening[a]	Day 1[b]	W 6	W 13	W 19	W 26	W 32	W 39	W 45	W 52
Visit Windows[c]		**12-16 Weeks After Last Infusion (Given at Week 65 of Previous Base Study)**	**±7 Days**							
Informed consent	X									
Procedures										
Demography	X									
Inclusion/exclusion criteria	X									
AEs and concomitant medication	X	X	X	X	X	X	X	X	X	X
Suicidality assessment	X	X[d]	X	X	X	X	X	X	X	X
Physical and neurological examinations	X		X		X				X	
Vital signs[e, f, g]	X	X	X	X	X	X	X	X	X	X
12-lead ECG	X								X	
Blood chemistry, hematology, and urinalysis	X		X		X		X		X	
Serum anti-bapineuzumab antibody[h]	X									X
Biochemical characterization[i]		X	X	X						
ADAS-Cog, DAD	X			X		X		X		X
NPI, DS, RUD-Lite v2.4, HUI	X					X				X
MMSE	X		X		X		X		X	
Clinical brain MRI[j]			X		X		X		X	

Table 1. Study Flowchart – 1st Year

First Year, Study Week (W)	Screening[a]	Day 1[b]	W 6	W 13	W 19	W 26	W 32	W 39	W 45	W 52
Visit Windows[c]		**12-16 Weeks After Last Infusion (Given at Week 65 of Previous Base Study)**	**±7 Days**							
Volumetric brain MRI[k]									X	
PIB PET imaging[k,l,m]									X	
Urine pregnancy test[n]									X	
CSF sample collection[k,o]										X
Infusion/infusion site assessment[p]		X		X		X		X		X
24 hours postinfusion phone contact		X		X		X		X		

ADAS-Cog = Alzheimer's Disease Assessment Scale–Cognitive Subscale; AE = adverse event; CSF = cerebrospinal fluid; DAD = Disability Assessment for Dementia; DS = Dependence Scale; ECG = electrocardiogram; HUI = Health Utilities Index; MMSE = Mini-Mental State Examination; MRI = magnetic resonance imaging; NPI = Neuropsychiatric Inventory; PET = positron emission tomography; PIB = [11C]-Pittsburgh compound B; RUD-Lite v2.4 = Resource Utilization in Dementia, version 2.4; W = week.

a. Screening visit for this study was the same visit as the Week 78 visit of the previous base study. Previous base study Week 78 procedures were not repeated; they are listed again here for reference purpose only. In addition, informed consent for this extension study was obtained before performing any procedures specific to this extension study. If the extension protocol was not yet initiated at a site at the Week 78 visit of the previous base study, the screening procedures specific to this study could be performed at another time point prior to Day 1.

b. With sponsor clinician review and approval, a subject received his first infusion between 16 and 26 weeks after the previous base study Week 65 visit (last infusion). The sponsor clinician could request additional screening evaluations as needed.

c. During the first year, follow-up visits (Weeks 6, 19, 32, and 45), including clinical brain MRI, were scheduled to occur 6 weeks after each infusion. These visits were to be scheduled relative to the actual infusion date and within the visit window (±7 days).

d. At Day 1, suicidality assessment was not mandatory if the previous suicidality assessment (screening visit) was conducted within 7 days before Day 1.

e. Vital signs included weight at all visits.

f. Sitting vital signs were to be measured at non-infusion visits.

g. Supine blood pressure and pulse were to be taken within 1 hour before dose administration and at 15, 30, 60 (end of infusion), and 120 minutes after the start of infusion. Temperature and respiratory rate were to be taken within 1 hour before dose administration, at 60 (end of infusion), and 120 minutes

Table 1. Study Flowchart – 1st Year

First Year, Study Week (W)	Screening[a]	Day 1[b]	W 6	W 13	W 19	W 26	W 32	W 39	W 45	W 52
Visit Windows[c]		12-16 Weeks After Last Infusion (Given at Week 65 of Previous Base Study)	±7 Days							

after the start of infusion. For Day 1 and Week 13, vital signs were measured 240 minutes (4 hours) after the start of infusion.

h. Blood sample for serum anti-bapineuzumab antibody was collected just prior to investigational product infusion.

i. Day 1 sample was collected after infusion; Week 13 sample was collected before infusion. Samples were collected at selected sites.

j. Central and local radiology review was required for all MRI scans. Both the local and central radiology reports had to be available and reviewed by the investigator prior to each investigational product infusion.

k. Only for subjects participating in the same substudies in the previous base study and who consented to continue in the substudies.

l. PET scans could be obtained within ±14 days of the visit. The PET scan schedule could 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 represented the maximum number of scans that each subject could receive. Details regarding local modifications to the PET scanning schedule were provided in the PET Clinical Imaging Manual.

m. Subjects in France were not allowed to participate in the PIB PET substudy.

n. Urine pregnancy test required prior to each PET scan only for female subjects aged <55 years who participated in the PET substudy.

o. CSF and associated blood samples could be collected within 4 weeks prior to the Week 52 visit.

p. Infusion site was assessed before dose and at 1 and 2 hours after the start of infusion start for all visits and also at 4 hours for Day 1 and Week 13.

Table 2. Study Flowchart – 2nd, 3rd, and 4th Year

2nd, 3rd and 4th Year Study Week (W)	W 65	W 78	W 91	W104	W117	W 130	W 143	W 156	W 169	W 182	W 195	W 208 or Early Termination (ET)
Visit Windows	**±7 Days**											
Procedures												
AEs and concomitant medications	X	X	X	X	X,	X	X	X	X	X	X	X
Suicidality assessment	X	X	X	X	X	X	X	X	X	X	X	X
Physical and neurological examinations		X		X		X		X		X		X
Vital signs[a]	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG				X				X				X
Blood chemistry, hematology, and urinalysis		X		X		X		X		X		X
Serum anti-bapineuzumab antibody[b]				X				X				X
ADAS-Cog, DAD		X		X		X		X		X		X
NPI, DS, RUD-Lite v2.4, HUI		X		X		X		X		X		X
Clinical brain MRI[c]		X		X		X		X		X		X
Volumetric brain MRI[d]				X				X				X
PIB PET imaging [d,e f]/Urine pregnancy test[g]				X				X				X
CSF sample collection[d]												X
Infusion/infusion site assessment[h]	X	X	X	X	X	X	X	X	X	X	X	
24 hours postinfusion phone contact	X	X	X	X	X	X	X	X	X	X	X	

ADAS-Cog = Alzheimer's Disease Assessment Scale–Cognitive Subscale; AEs = adverse event; CSF = cerebrospinal fluid; DAD = Disability Assessment for Dementia; DS = Dependence Scale; ECG = electrocardiogram; HUI = Health Utilities Index; MMSE = Mini-Mental State Examination; MRI = magnetic resonance imaging; NPI = Neuropsychiatric Inventory; PET = positron emission tomography; PIB = [11C]-Pittsburgh compound B; RUD-Lite v2.4 = Resource Utilization in Dementia, version 2.4; W = week.

a. Vital signs included weight at all visits. Supine blood pressure and pulse were taken within 1 hour before dose administration and at 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, after dose administration, and 120 minutes after the start of infusion. Sitting vital signs were taken at noninfusion visits (W 208 or ET).

b. Blood sample for serum anti-bapineuzumab antibody were collected just prior to investigational product infusion at W 104 and W 156.

c. Central and local radiology review was required for all MRI scans including ET. Both the local and central radiology reports had to be available and

Table 2. Study Flowchart – 2nd, 3rd, and 4th Year

2nd, 3rd and 4th Year Study Week (W)	W 65	W 78	W 91	W104	W117	W 130	W 143	W 156	W 169	W 182	W 195	W 208 or Early Termination (ET)
Visit Windows	**±7 Days**											

reviewed by the investigator prior to each investigational product infusion. Weeks 78, 104, 130, 156 and 182 MRI scans were scheduled ≥ 2 weeks prior to the visit.

d. Only for subjects participating in the same substudies in the previous base study and who consented to continue in the substudies.

e. PET scans could be obtained within 2 weeks before or after the date of the visit. The PET scan schedule could be 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 represented the maximum number of scans that each subject could have received. Details regarding local modifications to the PET scanning schedule were provided in the PET Clinical Imaging Manual.

f. Subjects in France were not allowed to participate in the PIB PET substudy.

g. A urine pregnancy test was only required for female subjects aged <55 years who participated in the PET substudy.

h. The infusion site was assessed before dose administration and at 1 and 2 hours after the start of infusion.

Table 3. Additional Schedule of Events for CSF Subset Subjects Only

Visit Description	CSF Tests	Blood Tests	CSF Local Laboratory Tests
Week 52 [a,b] 208 or ET	Y, Z, total-tau, phospho-tau	Z	Glucose, protein, WBCs, RBCs

CSF = cerebrospinal fluid; ET = early termination; Y = antibapineuzumab antibodies (CSF); Z = amyloid-beta protein (CSF, plasma); WBC = white blood cell; RBC = red blood cell.

a. When the lumbar puncture is scheduled at an infusion visit, the CSF and associated blood samples could be obtained within 4 weeks before the actual date of the visit.

b. Subjects enrolled before Protocol Amendment 1 (dated 26 July 2011) came into force and for whom CSF was not obtained at Week 52 would have CSF and associated blood samples collected at the Week 104 visit

Number of Subjects (Planned and Analyzed): A total of up to 800 subjects were estimated to continue from the previous base study into this study. A total of 506 subjects were screened and 492 were enrolled (216 from the previous base study placebo group and 276 from the previous base study bapineuzumab group). Fewer subjects than estimated were enrolled for a variety of reasons, including early discontinuation of the base study. Only 2 subjects completed this study due to its early discontinuation.

Diagnosis and Main Criteria for Inclusion: Male and female subjects who had completed the previous base study (Week 78) and with brain magnetic resonance imaging (MRI) scan from Week 71 consistent with the diagnosis of Alzheimer disease. Mini-Mental Status Examination ≥10 at screening and a caregiver able to attend all clinic visits with subject.

Exclusion Criteria: Subjects with any medical or psychiatric contraindication or clinically significant abnormality that, in the investigator's judgment, would substantially increase the risk associated with the subject's participation in and completion of the study or could preclude the evaluation of the subject's response; any significant Week 71 brain MRI abnormality; or subjects who had used any investigational drugs or devices, other than bapineuzumab within the last 60 days prior to screening.

Study Treatment: Bapineuzumab was supplied in single-use vials containing either 100 mg or 70 mg of bapineuzumab. Bapineuzumab 0.5 mg/kg was administered by IV infusion approximately every 13 weeks. The first investigational product infusion was on Day 1. Subsequent infusion visits were scheduled relative to Day 1, at Weeks 13, 26, 39, 52, 65, 78, 91, 104, 117, 130, 143, 156, 169, 182 and 195 as per the study schedule.

Safety Endpoint:

Primary Endpoint: To evaluate the long-term safety and tolerability of IV-administered bapineuzumab in subjects with AD.

Safety Evaluations: Safety and tolerability were evaluated from: incidence and severity of treatment-emergent adverse events (TEAEs) throughout the study; safety laboratory variables: clinical chemistry, hematology and urinalysis (analyzed centrally) including serum anti bapineuzumab antibodies; clinically important changes in vital signs, weight, electrocardiogram (ECGs) (readings/interpretations performed centrally), and physical and neurological examinations; brain MRI: all brain scans were read centrally and locally, and

reviewed prior to any subsequent investigational product infusion; suicidality assessment; and local reactions at the infusion site.

Statistical Methods: The Modified Intent-to-Treat (mITT) Population was defined as all randomly assigned subjects who received any amount of investigational product in the previous base study, who had a baseline for the previous base study and who had at least one valid postbaseline assessment of the Alzheimer's Disease Assessment Scale - Cognitive Subscale (ADAS-Cog) total score and Disability Assessment Scale for Dementia (DAD) total score in the previous base study and signed informed consent in this extension study.

The Extension mITT Population was defined as all randomly assigned subjects from the previous base study who received at least one dose of investigational product in this extension study and who had a baseline for this extension study and at least one valid postbaseline assessment of the ADAS-Cog total score and DAD total score in this extension study.

The Extension Positron Emission Tomography (PET) Population included all subjects enrolled in the PET substudy who received any amount of investigational product in this extension study, had a baseline PET assessment for the extension study and at least one postbaseline PET assessment in this extension study, and for whom at least three of the five regions of interest (anterior cingulate, posterior cingulate, frontal cortex, temporal cortex, and parietal cortex) had a ratio of target region radioactivity to reference region radioactivity (cerebellar grey matter) ≥1.35 at Baseline for the previous base study.

The Extension Cerebrospinal Fluid (CSF) Population included all subjects enrolled in the CSF substudy who received any amount of investigational product in this extension and had a baseline CSF assessment for this extension study and at least one postbaseline CSF measurement (CSF p-tau) in this extension study.

The Extension Volumetric MRI (vMRI) Population included all subjects enrolled in the vMRI substudy who received any amount of investigational product in this extension study and had a baseline vMRI assessment for this extension study and at least one postbaseline vMRI evaluation in this extension study.

The Safety Population included all subjects who consented to participate in this extension and received at least one dose of the investigational product (in this extension study).

All safety analyses were conducted on the safety population. Based on the treatment randomized to in the previous base study, the following treatment groups were used in the safety analyses:

- 0.5 mg/kg bapineuzumab + 0.5 mg/kg bapineuzumab;
- Placebo + 0.5 mg/kg bapineuzumab.

Safety data were summarized by the treatment subjects actually received (during the previous base study and this extension study). The number and percentage of TEAEs during the extension were summarized by treatment group. TEAEs in the extension study were defined

as AEs reported during this extension study that were either (1) not present at the start of the extension, or (2) were present at the start of the extension but worsened during the course of the extension. The same summaries were also provided for SAEs, AEs of special circumstance and deaths.

All AE terms and medical history were coded using the Medical Dictionary for Regulatory Activities dictionary (version 15.0).

Vital signs, ECGs and clinical laboratory evaluations were summarized by descriptive statistics, by treatment group, at all timepoints where these variables were collected. The descriptive statistics included means at each visit, mean changes from the Baseline Visit of the previous base study and mean changes from the final evaluation in the previous base study. The number and percentage of subjects with values of potential clinical importance were also summarized.

For subjects who received bapineuzumab in the previous base study, the primary baseline value of interest for vital signs, ECGs and laboratory evaluations was the baseline value from the previous base study (before bapineuzumab was given). For subjects who received placebo in the previous base study, the primary baseline value of interest was the final evaluation in the previous base study.

The potential TEAE of vasogenic edema (VE) was carefully evaluated. The incidence rate of VE with adjustment for patient exposure period was provided.

RESULTS

Subject Disposition and Demography: Subject disposition and analysis populations are provided in Table 4. The first subject was screened on 11 Dec 2009 and the last subject last visit was performed on 16 Oct 2012.

Table 4. Subject Disposition, Subjects Analyzed and Discontinuations From Treatment

Number (%) of Subjects	N	Placebo + 0.5 mg/kg Bapineuzumab (N=216)	0.5 mg/kg + 0.5 mg/kg Bapineuzumab (N=276)
Screened for extension study	506		
mITT[a]	506		
Randomized		216 (100)	276 (100)
Safety[b]		215 (99.5)	275 (99.6)
Extension mITT[c]		199 (92.1)	256 (92.8)
Extension PET[d, e]		1 (0.5)	0
Extension CSF[d]		9 (4.2)	6 (2.2)
Extension vMRI[d]		54 (25.0)	86 (31.2)
Subjects Received any amount of study treatment[f]		215 (99.5)	275 (99.6)
Subjects completed[g]		0	2 (0.7)
Subjects withdrawn from treatment[h]		216 (100)	274 (99.3)
Primary reason for withdrawal from treatment[i]			
Unsatisfactory response efficacy		3 (1.4)	6 (2.2)
Adverse event		17 (7.9)	12 (4.3)
Subject request		19 (8.8)	25 (9.1)
Investigator request		3 (1.4)	3 (1.1)
Death		3 (1.4)	1 (0.4)
Discontinuation of study by sponsor		164 (75.9)	217 (78.6)
Protocol violation		0	1 (0.4)
Failed to return		1 (0.5)	1 (0.4)
Lost to follow-up		1 (0.5)	1 (0.4)
Loss of caregiver		0	3 (1.1)
Other		4 (1.9)	4 (1.4)
Recurrent episode of VE		1 (0.5)	0

ADAS Cog = Alzheimer's Disease Assessment Scale - Cognitive Subscale; CSF = cerebrospinal fluid; DAD = Disability Assessment Scale for Dementia; mITT = modified Intent-to-Treat; N = number of subjects; PET = positron emission tomography; SUVr = standardized uptake value ratio; vMRI = volumetric magnetic resonance imaging; VE = vasogenic edema.

a. Defined as all randomly assigned subjects who received any amount of investigational product in the previous base study and who had a baseline for the previous base study and at least one valid postbaseline assessment of the ADAS Cog total score and DAD total score in the previous base study or this extension study and signed informed consent in this extension study.
b. Safety population is defined as all subjects who consented to participate in this extension and received at least one dose of study drug (in this extension study).
c. Defined as all randomly assigned subjects who received at least one dose of study drug in this extension study and who had a baseline for this extension study and at least one valid post baseline assessment of the ADAS Cog total score and DAD total score in this extension study.
d. Defined in general as those who enrolled in a given substudy in each row, in the safety population, and had a valid baseline and at least one postbaseline measurement in this extension study
e. Subject with a SUVr ≥1.35 at Baseline for the previous base study.
f. Any amount of study treatment represents at least one infusion or portion of an infusion.

Table 4. Subject Disposition, Subjects Analyzed and Discontinuations From Treatment

Number (%) of Subjects	N	Placebo + 0.5 mg/kg Bapineuzumab (N=216)	0.5 mg/kg + 0.5 mg/kg Bapineuzumab (N=276)

g. Subjects who did not terminate early from study treatment and completed the study up to and including Week 104.
h. Subjects who terminated early from treatment.
i. If subject discontinued from treatment and from the study, then reason for discontinuation from treatment was used for summary.

A summary of the subject demography and baseline characteristics by treatment sequence is presented in Table 5.

Table 5. Demographic and Baseline Characteristics, Safety Population

Characteristic	Placebo + 0.5 mg/kg Bapineuzumab (N=215)	0.5 mg/kg + 0.5 mg/kg Bapineuzumab (N=275)	Total (N=490)
Age (Years)			
< 65	44 (20.5)	42 (15.3)	86 (17.6)
≥65	171 (79.5)	233 (84.7)	404 (82.4)
Age (Years)			
N	215	275	490
Mean	71.4	72.1	71.8
Standard deviation	8.14	7.47	7.77
Median	72.0	72.0	72.0
Range	51-89	52-87	51-89
Sex			
Male	80 (37.2)	89 (32.4)	169 (34.5)
Female	135 (62.8)	186 (67.6)	321 (65.5)
Race			
Asian	39 (18.1)	63 (22.9)	102 (20.8)
Black	2 (0.9)	2 (0.7)	4 (0.8)
White	171 (79.5)	208 (75.6)	379 (77.3)
Other	3 (1.4)	2 (0.7)	5 (1.0)
Weight (kg)			
N	213	271	484
Mean	68.60	66.49	67.42
Standard deviation	14.342	15.597	15.079
Median	66.00	66.00	66.00
Range	39.0-108.0	34.4-130.0	34.4-130.0

N = number of subjects in each treatment group.

Efficacy Results: Efficacy measures were considered exploratory in this study and are not reported here due to the early discontinuation of this study.

Safety Results: The overview of the TEAEs is provided in Table 6. TEAEs in ≥2% of subjects in either group are presented in Table 7.

Table 6. Overview of Treatment Emergent Adverse Events - Safety Population

Category	Placebo + 0.5 mg/kg bapineuzumab (N=215) n (%)	0.5 mg/kg + 0.5 mg/kg bapineuzumab (N=275) n (%)
Subjects with AEs	152 (70.7)	184 (66.9)
Subjects with SAEs	35 (16.3)	33 (12.0)
Subjects with severe or life threatening AEs	17 (7.9)	19 (6.9)
Subjects discontinued from treatment due to AEs	18 (8.4)	10 (3.6)
Subjects discontinued from study due to AEs	14 (6.5)	10 (3.6)
Subjects with dose reduced or temporary discontinuation due to AEs	18 (8.4)	10 (3.6)
Subjects with treatment emergent deaths	5 (2.33)	2 (0.73)

Subjects were counted only once per treatment in each row.
Serious adverse events - according to the Investigator's assessment.
AE = adverse event; N = number of subjects in treatment group; n = number of subjects in each treatment group with specified criteria; SAE = serious adverse event.

Table 7. Treatment-Emergent Adverse Events reported by ≥2% of Subjects in Either Group (All Causalities) - Safety Population

Adverse Events by: System Organ Class Preferred Term	Placebo + 0.5 mg/kg bapineuzumab (N=215) n (%)	0.5 mg/kg + 0.5 mg/kg bapineuzumab (N=275) n (%)
Any treatment emergent adverse event	152 (70.7)	184 (66.9)
Gastrointestinal disorders	32 (14.9)	40 (14.5)
Diarrhoea	12 (5.6)	10 (3.6)
Nausea	2 (0.9)	6 (2.2)
Infections and infestations	56 (26.0)	53 (19.3)
Bronchitis	6 (2.8)	10 (3.6)
Nasopharyngitis	7 (3.3)	7 (2.5)
Upper respiratory tract infection	8 (3.7)	4 (1.5)
Urinary tract infection	12 (5.6)	9 (3.3)
Injury, poisoning and procedural complications	24 (11.2)	31 (11.3)
Fall	7 (3.3)	11 (4.0)
Musculoskeletal and connective tissue disorders	18 (8.4)	28 (10.2)
Arthralgia	4 (1.9)	8 (2.9)
Nervous system disorders	70 (32.6)	55 (20.0)
Cerebral microhaemorrhage	20 (9.3)	15 (5.5)
Headache	16 (7.4)	8 (2.9)
Syncope	5 (2.3)	2 (0.7)
Vasogenic cerebral oedema	23 (10.7)	10 (3.6)
Psychiatric disorders	35 (16.3)	40 (14.5)
Aggression	2 (0.9)	7 (2.5)
Agitation	5 (2.3)	8 (2.9)
Anxiety	11 (5.1)	7 (2.5)
Confusional state	3 (1.4)	7 (2.5)
Insomnia	4 (1.9)	6 (2.2)
Renal and urinary disorders	9 (4.2)	17 (6.2)
Pollakiuria	0	7 (2.5)
Respiratory, thoracic, and mediastinal disorders	6 (2.8)	14 (5.1)
Cough	4 (1.9)	6 (2.2)

AEs/SAEs 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 (v15.0) coding dictionary applied.
AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects in each treatment group; n = number of subjects in the treatment group with specific AE; SAE = serious adverse event; v = version.

Treatment related TEAEs were reported by 53 (24.7%) subjects in the placebo + bapineuzumab group and 48 (17.5%) in the bapineuzumab + bapineuzumab group (Table 8).

Table 8. Treatment-Emergent Adverse Events Reported by ≥2% of Subjects in Either Group (Treatment Related): Safety Population

Adverse Events by: System Organ Class Preferred Term	Placebo + 0.5 mg/kg bapineuzumab (N=215) n (%)	0.5 mg/kg + 0.5 mg/kg bapineuzumab (N=275) n (%)
Any treatment emergent adverse event	53 (24.7)	48 (17.5)
Nervous system disorders	43 (20.0)	29 (10.5)
Cerebral microhaemorrhage	16 (7.4)	13 (4.7)
Vasogenic cerebral oedema	23 (10.7)	10 (3.6)

AE/SAE results are not separated out.
Missing relatedness has been considered as related. If an event was reported as both related and unrelated for the same subject then it was considered related to study drug.
Denominators for percentages are the number of subjects in the safety population.
MedDRA (v15.0) coding dictionary applied.
AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects in each treatment group; n = number of subjects in the treatment group with specific AE; SAE = serious adverse event; v = version.

Serious Adverse Events: Treatment-emergent SAEs were reported in 35 (16.3%) subjects in the placebo + bapineuzumab group and 33 (12.0%) subjects in the bapineuzumab + bapineuzumab group.

Treatment emergent SAEs (all causalities) in subjects in either group are presented in Table 9.

Table 9. Treatment-Emergent Serious Adverse Events (All Causalities), Safety Population

Adverse Events by: System Organ Class Preferred Term	Placebo + 0.5 mg/kg Bapineuzumab (N=215) n (%)	0.5 mg/kg + 0.5 mg/kg Bapineuzumab (N=275) n (%)
Any treatment emergent serious adverse event	35 (16.3)	33 (12.0)
Cardiac disorders	3 (1.4)	3 (1.1)
Aortic valve stenosis	1 (0.5)	0
Atrial flutter	1 (0.5)	0
Atrioventricular block	1 (0.5)	0
Cardiac failure	1 (0.5)	1 (0.4)
Cardiac failure congestive	1 (0.5)	1 (0.4)
Cardiomyopathy	0	1 (0.4)
Mitral valve disease	1 (0.5)	0
Gastrointestinal disorders	4 (1.9)	3 (1.1)
Abdominal pain	0	1 (0.4)
Gastrointestinal haemorrhage	2 (0.9)	0
Gastrooesophageal reflux disease	0	1 (0.4)
Haemorrhoidal haemorrhage	0	1 (0.4)
Haemorrhoids	1 (0.5)	0
Pancreatitis	1 (0.5)	0
General disorders and administration site conditions	0	4 (1.5)
Asthenia	0	1 (0.4)
Chest pain	0	1 (0.4)
Gait disturbance	0	1 (0.4)
General physical health deterioration	0	1 (0.4)
Hepatobiliary disorders	2 (0.9)	0
Cholelithiasis	1 (0.5)	0
Hepatic steatosis	1 (0.5)	0
Infections and infestations	4 (1.9)	4 (1.5)
Bronchitis	0	1 (0.4)
Gastritis viral	1 (0.5)	0
Lower respiratory tract infection	0	1 (0.4)
Peritonsillar abscess	1 (0.5)	0
Pneumonia	0	1 (0.4)
Urinary tract infection	2 (0.9)	1 (0.4)
Injury, poisoning and procedural complications	3 (1.4)	5 (1.8)
Alcohol poisoning	1 (0.5)	0
Fall	1 (0.5)	0
Femur fracture	0	1 (0.4)
Forearm fracture	0	1 (0.4)
Hip fracture	0	1 (0.4)
Lower limb fracture	0	1 (0.4)
Lumbar vertebral fracture	1 (0.5)	0
Subdural haematoma	1 (0.5)	0
Traumatic intracranial haemorrhage	1 (0.5)	0
Wrist fracture	0	1 (0.4)
Investigations	0	1 (0.4)
Blood creatinine increased	0	1 (0.4)
Musculoskeletal and connective tissue disorders	1 (0.5)	1 (0.4)
Arthralgia	0	1 (0.4)
Muscular weakness	1 (0.5)	0

Table 9. Treatment-Emergent Serious Adverse Events (All Causalities), Safety Population

Adverse Events by: System Organ Class Preferred Term	Placebo + 0.5 mg/kg Bapineuzumab (N=215) n (%)	0.5 mg/kg + 0.5 mg/kg Bapineuzumab (N=275) n (%)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	3 (1.4)	3 (1.1)
Bladder neoplasm	0	1 (0.4)
Gastric cancer	0	1 (0.4)
Metastases to lymph nodes	1 (0.5)	0
Metastases to peritoneum	1 (0.5)	0
Ovarian cancer	1 (0.5)	0
Pancreatic carcinoma	1 (0.5)	0
Squamous cell carcinoma of skin	0	1 (0.4)
Nervous system disorders	16 (7.4)	10 (3.6)
Carotid artery stenosis	0	1 (0.4)
Cerebellar infarction	0	1 (0.4)
Cerebral haemorrhage	1 (0.5)	0
Cerebral infarction	1 (0.5)	0
Cerebral microhaemorrhage	2 (0.9)	0
Cerebrovascular accident	1 (0.5)	0
Convulsion	1 (0.5)	2 (0.7)
Epilepsy	3 (1.4)	0
Ischaemic stroke	1 (0.5)	1 (0.4)
Lacunar infarction	1 (0.5)	0
Lumbar radiculopathy	0	1 (0.4)
Multiple system atrophy	0	1 (0.4)
Partial seizures	0	1 (0.4)
Presyncope	1 (0.5)	0
Subarachnoid haemorrhage	2 (0.9)	0
Vasogenic cerebral oedema	6 (2.8)	2 (0.7)
Psychiatric disorders	2 (0.9)	6 (2.2)
Aggression	1 (0.5)	2 (0.7)
Agitation	1 (0.5)	2 (0.7)
Confusional state	0	2 (0.7)
Delusion	0	1 (0.4)
Hallucination	0	1 (0.4)
Mental status changes	0	1 (0.4)
Mood swings	0	1 (0.4)
Suicidal ideation	0	1 (0.4)
Renal and urinary disorders	0	1 (0.4)
Incontinence	0	1 (0.4)
Skin and subcutaneous tissue disorders	0	1 (0.4)
Urticaria	0	1 (0.4)
Vascular disorders	0	1 (0.4)
Peripheral artery stenosis	0	1 (0.4)

Denominators for percentages are the number of subjects in the safety population.
Subjects were counted only once per treatment in each row.
MedDRA (v15.0) coding dictionary applied.
MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects in each treatment groups; n = number of subjects in the treatment group with specific AE; v = version.

Discontinuations: Overall, TEAEs that led to discontinuation of treatment were reported in 18 (8.4%) subjects in the placebo + bapineuzumab group and 10 (3.6%) subjects in the bapineuzumab + bapineuzumab group. The most common TEAEs that led to discontinuation from treatment involved nervous system disorders, reported in 11 (5.1%) subjects in the placebo + bapineuzumab group and 6 (2.2%) subjects in the bapineuzumab + bapineuzumab group, of which 4 (1.9% and 1.5%, respectively) subjects in each group experienced vasogenic cerebral edema. (Table 10).

Table 10. Treatment-Emergent Adverse Events That Led to Discontinuation of Treatment, Safety Population

Adverse Events by: System Organ Class Preferred Term	Placebo + 0.5 mg/kg Bapineuzumab (N=215) n (%)	0.5 mg/kg + 0.5 mg/kg Bapineuzumab (N=275) n (%)
Any TEAE that led to discontinuation of treatment	18 (8.4)	10 (3.6)
Cardiac disorders	2 (0.9)	1 (0.4)
Cardiac failure	1 (0.5)	1 (0.4)
Mitral valve disease	1 (0.5)	0
Injury, poisoning and procedural complications	1 (0.5)	1 (0.4)
Lower limb fracture	0	1 (0.4)
Subdural haemorrhage	1 (0.5)	0
Metabolism and nutrition disorders	2 (0.9)	0
Decreased appetite	1 (0.5)	0
Haemosiderosis	1 (0.5)	0
Neoplasms benign, malignant and unspecified (including cysts and polyps)	2 (0.9)	0
Metastases to lymph nodes	1 (0.5)	0
Pancreatic carcinoma	1 (0.5)	0
Nervous system disorders	11 (5.1)	6 (2.2)
Cerebral haemosiderin deposition	1 (0.5)	0
Cerebral infarction	1 (0.5)	0
Cerebral microhaemorrhage	1 (0.5)	0
Epilepsy	2 (0.9)	0
Ischaemic stroke	1 (0.5)	1 (0.4)
Multiple system atrophy	0	1 (0.4)
Subarachnoid haemorrhage	1 (0.5)	0
Vasogenic cerebral oedema	4 (1.9)	4 (1.5)
Psychiatric disorders	0	1 (0.4)
Agitation	0	1 (0.4)
Skin and subcutaneous tissue disorders	0	1 (0.4)
Urticaria	0	1 (0.4)

Denominators for percentages are the number of subjects in the safety population.
Subjects were counted only once per treatment in each row.
MedDRA (v15.0) coding dictionary applied.
MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects in each treatment group; n = number of subjects in the treatment group with specific AE; TEAE = treatment emergent adverse event; v = version.

Overall, TEAEs that led to discontinuation of the study (as opposed to discontinuation of treatment while remaining in the study) were reported in 14 (6.5%) subjects in the placebo + bapineuzumab group and 10 (3.6%) subjects in the bapineuzumab + bapineuzumab group. The most common TEAEs that led to discontinuation of the study involved nervous

system disorders, reported in 6 (2.8%) subjects in the placebo + bapineuzumab group and 4 (1.5%) subjects in the bapineuzumab + bapineuzumab group, of which 1 (0.5%) and 3 (1.1%) subjects, respectively, experienced vasogenic cerebral edema. TEAEs that led to discontinuation of the study are presented in Table 11.

Table 11. Treatment-Emergent Adverse Events That Led to Discontinuation of Study, Safety Population

Adverse Events by: System Organ Class Preferred Term	Placebo + 0.5 mg/kg Bapineuzumab (N=215) n (%)	0.5 mg/kg + 0.5 mg/kg Bapineuzumab (N=275) n (%)
Any TEAE that led to discontinuation of study	14 (6.5)	10 (3.6)
Cardiac disorders	2 (0.9)	1 (0.4)
Atrial flutter	1 (0.5)	0
Cardiac failure	1 (0.5)	1 (0.4)
Injury, poisoning and procedural complications	1 (0.5)	1 (0.4)
Lower limb fracture	0	1 (0.4)
Subdural haemorrhage	1 (0.5)	0
Metabolism and nutrition disorders	2 (0.9)	0
Decreased appetite	1 (0.5)	0
Haemosiderosis	1 (0.5)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	3 (1.4)	0
Metastases to lymph nodes	1 (0.5)	0
Ovarian cancer	1 (0.5)	0
Pancreatic carcinoma	1 (0.5)	0
Nervous system disorders	6 (2.8)	4 (1.5)
Cerebral haemosiderin deposition	1 (0.5)	0
Cerebral microhaemorrhage	1 (0.5)	0
Epilepsy	2 (0.9)	0
Ischaemic stroke	1 (0.5)	0
Multiple system atrophy	0	1 (0.4)
Vasogenic cerebral oedema	1 (0.5)	3 (1.1)
Psychiatric disorders	0	4 (1.5)
Aggression	0	1 (0.4)
Agitation	0	2 (0.7)
Mood swings	0	1 (0.4)

Denominators for percentages are the number of subjects in the safety population.
Subjects were counted only once per treatment in each row.
MedDRA (v15.0) coding dictionary applied.
MedDRA = Medical Dictionary for Regulatory Activities; n = number of subjects in the treatment group with specific AEs; N = number of subjects in each treatment group; TEAE = treatment emergent adverse event; v = version.

Deaths: A total of 8 subjects died overall: 6 in the placebo + bapineuzumab group and 2 in the bapineuzumab + bapineuzumab group. Of these deaths, 1 was not treatment-emergent. Of the 7 deaths due to TEAEs, 1 was due to a TEAE that was assessed as related to treatment (subarachnoid haemorrhage in the placebo + bapineuzumab group). TEAEs that resulted in death are presented in Table 12.

Table 12. Treatment Emergent Adverse Events That Led to Death, Safety Population

Adverse Events by: System Organ Class Preferred Term	Bapineuzumab	
	Placebo + 0.5 mg/kg (N=215)	0.5 mg/kg + 0.5 mg/kg (N=275)
	n (%)	n (%)
Any treatment-emergent adverse events that led to death	5 (2.3)	2 (0.7)
Cardiac disorders	1 (0.5)	2 (0.7)
Cardiac failure	1 (0.5)	0
Cardiac failure congestive	0	1 (0.4)
Cardiomyopathy	0	1 (0.4)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	3 (1.4)	0
Metastases to lymph nodes	1 (0.5)	0
Ovarian cancer	1 (0.5)	0
Pancreatic carcinoma	1 (0.5)	0
Nervous system disorders	1 (0.5)	0
Subarachnoid haemorrhage	1 (0.5)	0

Denominators for percentages are the number of subjects in the Safety Population.
Subjects were counted only once per treatment in each row.
MedDRA (v15.0) coding dictionary applied.
MedDRA = Medical dictionary for regulatory activities; N = number of subjects in each treatment group; n = number of subjects in treatment group with specific AEs; v = version.

Laboratory Evaluation: Small percentages of subjects had reductions from normal baseline values to low postbaseline values in hematocrit (1.4% and 1.1%), hemoglobin (2.8% and 2.5%), lymphocyte count (3.3% and 1.8%), and glucose (0.9% and 1.5%), in the placebo + bapineuzumab and bapineuzumab + bapineuzumab groups respectively.

Small percentages of subjects had reductions from extension study baseline normal values to extension study low minimum postbaseline values for these same parameters: hematocrit (1.4% and 1.5%), hemoglobin (2.8% and 2.2%), lymphocyte count (2.3% and 1.5%), and glucose (0.9% and 1.5%), in the placebo + bapineuzumab and bapineuzumab + bapineuzumab groups respectively.

Small percentages of subjects had increases from normal baseline values to high postbaseline values for: alanine aminotransferase (ALT) (1.4% and 1.5%), aspartate aminotransferase (AST) (1.4% and 0.4%), glucose (1.4% and 3.6%), potassium (1.4% and 1.5%), bilirubin total (0.5% and 1.5%), and uric acid (0.5% and 2.9%), in the placebo + bapineuzumab and bapineuzumab + bapineuzumab groups respectively.

Small percentages of subjects had increases from extension study baseline normal values to extension study high maximum postbaseline values for: ALT (0.5% and 1.1%), AST (0.9% and 0%), glucose (0.9% and 2.5%), potassium (1.4% and 1.5%), bilirubin total (0.5% and 0.7%), and uric acid (0.5% and 2.5%), in the placebo + bapineuzumab and bapineuzumab + bapineuzumab groups respectively.

Vital Signs and ECG: Transient changes were observed in diastolic and systolic blood pressure, pulse rate, respiratory rate and weight but no clinically relevant abnormal trends were noted. Transient reductions in temperature and weight were observed but no significant trends were noted. No clinically relevant abnormal trends in ECG results were noted.

CONCLUSION: IV infusion of bapineuzumab 0.5 mg/kg every 13 weeks for up to approximately 3 years (base study + extension study) was generally well tolerated, with a safety and tolerability profile that was similar to that observed in previous studies of bapineuzumab. No new or unexpected safety concerns were identified.