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GENERIC DRUG NAME / COMPOUND NUMBER: Ponezumab / PF-04360365

PROTOCOL NO: A9951002

PROTOCOL TITLE: A Phase 2 Multicenter, Randomized, Double-Blind, Placebo-Controlled Study of the Safety, Tolerability, and Pharmacokinetics of Multiple Doses of PF-04360365 in Patients With Mild-to-Moderate Alzheimer's Disease

Study Centers: A total of 30 centers took part in the study and randomized subjects; 4 each in Australia and Belgium, 7 in Canada, 3 in the United Kingdom (UK), and 6 each in the Republic of Korea and the United States of America (USA).

Study Initiation Date and Final Completion Date: 05 December 2008 to 16 August 2011

Phase of Development: Phase 2

Study Objectives:

Primary Objectives:

- To examine the safety and tolerability of PF-04360365 (ponezumab) in subjects with mild-to-moderate Alzheimer's disease (AD) dosed for 18 months and followed for a total of 24 months.
- To characterize the pharmacokinetics (PK) of ponezumab following administration of multiple doses in subjects with mild-to-moderate AD.

Secondary Objectives:

- To examine the efficacy of ponezumab, as assessed by the 70 point Alzheimer's disease Assessment Scale-Cognitive Subscale (ADAS-cog) and Disability Assessment for Dementia (DAD) scales, in subjects with mild-to-moderate AD.
- To determine the effect of ponezumab on the following biochemical markers: Aβ-species in cerebrospinal fluid (CSF) and plasma; CSF tau and phospho-tau (p-tau) levels.
- To examine the effect of ponezumab on CSF safety labs in the subset of subjects receiving lumbar punctures.
- To determine the immunogenicity of ponezumab following repeat dosing.
- To evaluate the PK/pharmacodynamic (PD) relationships for Aβ biomarkers, ADAS-cog DAD and electrocardiogram (ECG).

METHODS

Study Design: This was a multiple-dose, randomized, double-blinded, and placebo-controlled, safety, tolerability, and PK/PD study in subjects with mild-to-moderate AD.

Part A of the study was planned to be conducted in approximately 100 participants diagnosed with mild-to-moderate AD (Screening Mini-Mental State Examination [MMSE] scores of 16 to 26, inclusive). Participants were randomized in a 1:1:1:1 ratio to 1 of 3 doses of ponezumab or placebo (25 subjects in each of 4 treatment groups) and dosed with investigational drug approximately every 60 days for 18 months (10 doses). Subjects received ponezumab 0.1 mg/kg, ponezumab 0.5 mg/kg, ponezumab 1.0 mg/kg, or placebo. All subjects, regardless of the number of doses received, were encouraged to remain in the study and complete the planned assessments through the Month 24 visit.

Part B of the study was an extension of Part A whereby an additional group of placebo subjects and 2 additional ponezumab dose levels were investigated. Enrollment in Part B commenced upon completion of enrollment of the 100 subjects required for Part A of the study. Part B of the study was planned to be conducted in approximately 75 participants diagnosed with mild-to-moderate AD. Participants were randomized in a 1:1:1 ratio to 1 of 2 doses of ponezumab or placebo (25 subjects in each of 3 treatment groups) and dosed with investigational drug approximately every 60 days for 18 months (10 doses). Subjects received ponezumab 3.0 mg/kg, ponezumab 8.5 mg/kg, or placebo. The doses chosen for this study were predicted to achieve and maintain exposures below that seen with the 10 mg/kg ponezumab dose studied previously.

The schedule of activities is provided in Table 1. Due to duration of the study, visits have been described in Table 1 both by month and study day. Study days were days postdose where Month 0, Day 1 refers to the day of first dose.

Table 1. Schedule of Activities

Visit Dates (in Months)	Screening Day-60 to Day 0	Baseline Day-7 to Day 0[a]	Predose: Day of Dosing for All Dosing Dates: 0, 2, 4, 6, 8, 10, 12, 14, 16, 18	Postdose: Day of Dosing Visits for All Dosing Dates: 0, 2, 4, 6, 8, 10, 12, 14, 16, 18	Postdose Telephone Follow-Up 1, 9, 11, 15, 17, 21, 23[b]	Postdose Follow-Up 3, 5, 7, 13	Month 19	Month 22	Month 24	Early Termina-tion[c]
Visit Dates (in Days; Based on 30 Days per Month)	**Day-60 to Day 0**	**Day-7 to Day 0**	**1, 60, 120, 180, 240, 300, 360, 420, 480, 540**	**1, 60, 120, 180, 240, 300, 360, 420, 480, 540**	**30, 270, 330, 450, 510, 630, 690**	**90, 150, 210, 390**	**570**	**660**	**720**	
Visit Windows				**±10 Days[d]**	**±4 Days for Day 30 and ±10 Days for All Other Visits**	**±10 Days**	**±10 Days**	**±10 Days**	**+10 Days**	
Telephone Visit					**X**					
Sign informed consent form/provide assent	X									
Review inclusion/exclusion	X	X	X							
Complete medical history	X									
Full physical/neurological examinations	X								X	X
Brief physical/neurological examination			X			X	X			
Rosen-modified hachinski ischemia	X									
Concomitant medications	X		X		X	X	X	X	X	X
Weight	X	X	X			X	X		X	X
Vital signs (supine)	X	X	X	X		X	X	X	X	X
Adverse event assessments		X	X	X	X	X	X	X	X	X

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Visit Windows				**±10 Days[d]**	**±4 Days for Day 30 and ±10 Days for All Other Visits**	**±10 Days**	**±10 Days**	**±10 Days**	**+10 Days**	
Telephone Visit					**X**					
Study drug administration				X						
ApoE genotyping		X								
ADAS-cog, MMSE, DAD, NTB, CogState, and NPI	MMSE/ CogState only	X				3, 7, 13	X		X	X
CDR/CDR-SB (should be performed on separate visit day-split visit)		X					X			X
EQ-5D/ Residence status item		X				13	X		X	X
Safety laboratories/ electrocardiogram[e]	X	Labs only	X			3, 7, 13	X		X	X
Telemetry			X	X						
MRI	X					3, 7, 13[f]	X		X	X
Pharmacokinetic blood and urine sampling			X[g,h]	X[h,i]		X	X	X	X	X
Pharmacodynamic sampling (includes blood and urine collection)			X[g,h]	X[h,i]		X	X	X	X	X

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Visit Windows				**±10 Days[d]**	**±4 Days for Day 30 and ±10 Days for All Other Visits**	**±10 Days**	**±10 Days**	**±10 Days**	**+10 Days**	
Telephone Visit					**X**					
Immunogenicity sampling			X[g]			X	X	X	X	X
Optional lumbar puncture (cerebrospinal fluid)		X				3[f]	X[f]			
Sample banking for exploratory research[j]		X (CSF, blood/ urine)				3 (CSF only), 13 (blood/ urine)	X (CSF/ blood/ urine)			

ApoE = apolipoprotein E; ADAS-cog = Alzheimer's Disease Assessment Scale-Cognitive Subscale; CDR = Clinical Dementia Rating Scale; CDR-SB = Clinical Dementia Rating Scale-Sum of Boxes; CogState = Cognitive State Battery; CSF = cerebrospinal fluid; DAD = Disability Assessment for Dementia; EQ-5D = EuroQol-5D; ECG = electrocardiogram; IEC = independent ethics committee; IRB = institutional review board; Lab = laboratory; MMSE = Mini-Mental State Examination; MRI = magnetic resonance imaging; NTB = Neuropsychological Test Battery; NPI = Neuropsychiatric Inventory (questionnaire).

a. If the baseline assessments were performed on more than 1 day, the 7-Day window began on the day that the final baseline assessment result was received. In the event that a baseline assessment needed to be repeated, the 7-Day window began at the time that the last repeat baseline result was received.
b. Per the Investigator's discretion, telephone visits may have been conducted as face-to-face office visits either instead of a telephone visit or based on the telephone conversation with the subject and/or caregiver.
c. If necessary for subjects who terminated study prior to completion.
d. The minimum dosing interval was 50 days. A subject may have been dosed up to 10 days late or 10 days early. If a dose was missed and it was beyond the 10 Day window, subjects were dosed at the next scheduled dose date and the total number of study drug administrations would have been reduced.
e. Predose safety laboratory assessments could have been performed predose the Day of dosing; ECG should have been performed predose on the Day of dosing; postdose ECGs should have been taken immediately after pharmacokinetic/pharmacodynamic sampling following completion of infusion; ECGs should have been performed immediately at the end of infusion (at approximately Hour 2 from the start of infusion) and at approximately Hour 6 (4 hours after the completion of infusion on the Day of dosing.
f. MRI preliminary reading results must have been available and determined not clinically significant prior to lumbar puncture; visits at Months 3 and 19 may have been split to

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Visit Windows				±10 Days[d]	±4 Days for Day 30 and ±10 Days for All Other Visits	±10 Days	±10 Days	±10 Days	+10 Days	
Telephone Visit					X					

allow lumbar puncture to be performed up to 10 days following visits (+10 days) within the study window. The lumbar puncture may not have been performed prior to the MRI. Lumbar puncture was performed after all cognitive assessments.

g. Blood sample was taken immediately before study drug infusion; blood samples were taken from the arm that was not receiving the infusion of study drug.
h. One urine sample was taken before drug infusion and another urine sample was taken after completion of infusion at the time of first void after dosing and prior to discharge.
i. Blood sample was taken immediately after completion of infusion at approximately 2 hours after the start of infusion; samples must have been taken from the arm that was not receiving the infusion of study drug.
j. Subject to IRB/ IEC approval and subject consent.

Number of Subjects (Planned and Analyzed): Approximately 100 subjects were planned to be enrolled in the study for Part A. Of 286 subjects screened, 198 subjects (14 in Australia, 11 in Belgium, 91 in Canada, 53 in the Republic of Korea, 8 in the UK and 21 in the USA) were randomized. A total of 103 subjects were assigned to study treatment and 99 subjects were treated in Part A of the study. Approximately 75 subjects were planned to be enrolled for Part B; 95 subjects were assigned to study treatment and treated in Part B of the study.

Diagnosis and Main Criteria for Inclusion and Exclusion: Male and female (of non-childbearing potential) subjects aged ≥50 years with a diagnosis of probable AD, consistent with criteria from both the National Institute of Neurological and Communicative Disorders and Stroke and AD and Related Disorders Association; and Diagnostic and Statistical Manual of Mental Disorders, with an MMSE score of 16-26 inclusive and a Rosen-Modified Hachinski Ischemia Score ≤4.

Main Exclusion Criteria: Subjects with diagnosis or history of other dementia or neurodegenerative disorders; diagnosis or history of clinically significant cerebrovascular disease; specific findings on MRI; cortical infarct, micro hemorrhage, multiple white matter lacunes, extensive white matter abnormalities; history of autoimmune disorders; history of allergic or anaphylactic reactions were excluded.

Study Treatment: Ponezumab or placebo was administered as a continuous intravenous infusion over approximately 2 hours approximately every 60 days. ponezumab (or placebo) was diluted into 0.9% sodium chloride injection prior to administration. In Part A of the study, subjects were assigned to the ponezumab 0.1, 0.5, or 1.0 mg/kg dose level or to placebo in a 1:1:1:1 ratio. In Part B of the study, subjects were assigned to the ponezumab 3.0 or 8.5 mg/kg dose level or to placebo in a 1:1:1 ratio.

Safety, Efficacy, Pharmacokinetics and Pharmacodynamics Endpoints:

Primary Endpoints:

- Safety endpoints included adverse events (AEs), physical/neurological exams, vital signs, 12-lead electrocardiogram (ECG), clinical laboratory values, brain magnetic resonance imaging (MRI) and cognitive assessments.
- Plasma and CSF concentrations (as available) of ponezumab.

Secondary Endpoints:

- Change from Baseline on ADAS-cog and the DAD total scores at Month 19.
- Plasma and CSF concentrations of Aβ species.
- CSF concentrations of tau and p-tau.
- Change from Baseline in CSF protein, red blood cells (RBCs), white blood cells (WBCs), and glucose.

- Immunogenicity quantified as anti-drug antibodies (ADAs).

Safety Evaluations: Clinical monitoring, vital signs (heart rate, blood pressure [BP]), body weight, 12-lead ECGs, AEs, safety laboratory tests, physical examinations, neurological examinations, brain MRI (if the Investigator determined this was necessary), continuous cardiac monitoring by telemetry (for abnormal rhythms), and immunogenicity.

Statistical Methods:

Full Analysis Set (FAS): The FAS consisted of all participants who were randomized and received at least 1 infusion of study medication.

Per-Protocol (PP) Analysis Set: The PP set consisted of all participants within the FAS who had received at least 9 infusions of study drug, undergone the scheduled or windowed efficacy assessment at Baseline and the Month 19 (Day 570) visit.

Safety Analysis Set: The safety set consisted of all subjects who had received an infusion of study medication (including partial infusions).

All subjects who received at least 1 infusion of study medication were included in the analyses and listings of the PK endpoints.

Analysis of Efficacy Parameters: Baseline was defined as the last assessment for the endpoint prior to the first study drug infusion. Two-sided hypothesis tests comparing each active treatment with placebo were conducted for each endpoint at the nominal α=0.10 level without adjustment for multiple treatment contrasts or multiple endpoints. Least square (LS) means, with standard errors, for the change from Baseline and treatment differences from placebo of the change from Baseline were calculated and presented with 90% confidence intervals (CIs). The CIs were not adjusted for multiplicity and were used to help assess the precision of the estimates.

The Mixed Model Repeated Measures (MMRM) approach was applied to compare the mean change from Baseline for ADAS-cog total score, DAD total score, MMSE total score, CogState individual tasks and composite score, neuropsychological test battery individual tests and composite score, neuropsychiatric inventory total score, EuroQol-5D visual analogue scale, and brain volumes between each active dose and placebo for each visit. The primary assessment was the change from Baseline at the Month 19 visit (approximately 30 days following the last study drug infusion), using the FAS. The fixed effects in the model were time (as categorical), treatment, treatment-by-time interaction, baseline value, and country. An unstructured variance-covariance matrix was assumed for the within-subject errors. Analysis of covariance was used to compare the mean change from Baseline for Clinical Dementia Rating Scale-Sum of Boxes (CDR-SB) between each active dose and placebo at Month 19 using the FAS. The effects in the model were treatment, Baseline CDR-SB, and country.

Analysis of PK Parameters: Ponezumab concentrations in plasma, CSF and urine were listed and summarized at each time point by dose level using descriptive statistics and graphical presentation. The accumulation of ponezumab after administration of multiple doses was

assessed using the ratio of (concentration at the end of the infusion [$C_{end,inf}$] at steady state [Month 18])/ ($C_{end,inf}$ after the first dose [Month 0]) and the ratio of (trough concentration [C_{trough}] at steady state [Month 18])/(C_{trough} after the first dose [Month 2]).

Analysis of PD Parameters: Plasma and CSF Aβ biomarkers, tau, and p-tau concentration-time data were listed and summarized by dose using descriptive statistics and graphical presentation. In addition, the percent change from Baseline in CSF Aβ biomarkers, tau, and p-tau at Months 3 and 19 following the initiation of blinded therapy (ponezumab or placebo) were summarized by dose using descriptive statistics.

Analysis of Safety Parameters: Safety parameters were analyzed descriptively.

RESULTS:

Subject Disposition and Demography: A summary of subject disposition is provided in Table 2. Four (4) subjects were randomized (Part A), but did not receive study drug. A total of 194 subjects were treated of which 146 subjects completed the study and 48 subjects discontinued. A total of 20 subjects discontinued from the study due to an AE. A total of 19 subjects discontinued study treatment due to an AE. One (1) subject completed treatment, but discontinued from the study during the follow-up period due to an AE that resulted in death. A total of 10 subjects discontinued from the study due to an AE. Discontinuations from the study are summarized in Table 3.

Table 2. Subject Disposition

Number of Subjects	Part A				Part B		
	Ponezumab 0.1 mg/kg	Ponezumab 0.5 mg/kg	Ponezumab 1.0 mg/kg	Placebo Part A	Ponezumab 3.0 mg/kg	Ponezumab 8.5 mg/kg	Placebo Part B
Screened: 286							
Assigned to study treatment	26	26	25	26	32	31	32
Treated	25	25	25	24	32	31	32
Completed	21	20	18	18	23	20	26
Discontinued	4	5	7	6	9	11	6
During double-blind treatment period	3	4	7	6	8	8	6
During post-therapy follow-up	1	1	0	0	1	3	0

Table 3. Discontinuations From the Study

Number of Subjects	Part A				Part B		
	Ponezumab 0.1 mg/kg	Ponezumab 0.5 mg/kg	Ponezumab 1.0 mg/kg	Placebo Part A	Ponezumab 3.0 mg/kg	Ponezumab 8.5 mg/kg	Placebo Part B
Withdrawal phase: during double-blind treatment period	3	4	7	6	8	8	6
Subject died	0	0	0	0	0	0	2
No longer willing to participate in study	2	3	4	4	4	6	3
Protocol violation	1	0	0	0	0	1	0
Other	0	0	1	1	2	0	1
Treatment-related adverse event	0	0	0	0	1	0	0
Adverse event not related to study drug	0	1	2	1	1	1	0
Withdrawal phase: during post-therapy follow-up	1	1	0	0	1	3	0
Subject died	0	1	0	0	0	0	0
No longer willing to participate in study	1	0	0	0	0	1	0
Other	0	0	0	0	1	2	0

A summary of demographic characteristics is provided in Table 4. Demographic characteristics were similar among the treatment groups. Subjects included male and female (89 male subjects and 105 female subjects) adults who had mild-to-moderate AD. Subjects ranged in age from 51 to 90 years of age, ranged in weight from 38.6 to 100 kg, and had a total mean body mass index ranging from 17.7 to 47.0 kg/m^2.

Table 4. Demographic Characteristics

	Ponezumab 0.1 mg/kg (N=25)	Ponezumab 0.5 mg/kg (N=25)	Ponezumab 1.0 mg/kg (N=25)	Placebo Part A (N=24)	Ponezumab 3.0 mg/kg (N=32)	Ponezumab 8.5 mg/kg (N=31)	Placebo Part B (N=32)
Gender, n							
Male	13	10	14	11	12	14	15
Female	12	15	11	13	20	17	17
Age (years)							
Mean	70.8 (8.2)	71.9 (9.4)	72.2 (8.4)	70.0	70.5 (8.9)	71.8 (7.3)	70.4
(SD)				(7.8)			(10.3)
Range	54-84	51-86	52-83	55-83	52-86	58-85	52-90

N = number of subjects; n = number of subjects with specified criteria; SD = standard deviation.

Efficacy, Pharmacokinetics and Pharmacodynamics Results:

Plasma and CSF Concentrations (as Available) of Ponezumab: The mean plasma drug levels for ponezumab revealed dose-dependent increases in exposure that were maintained over the duration of the study. There was limited accumulation following multiple dose administration of ponezumab; mean increases were approximately 1.0- to 1.3-fold based on $C_{end, inf}$, Month 18/$C_{end, inf}$, Month 0, and 1.5- to 1.8-fold based on C_{trough}, Month 18/$C_{trough,}$ Month 2.

Ponezumab concentrations in CSF at Months 3 and 19 postdose were below the lower limit of quantification (LLOQ) of the bioanalytical assay (12.0 ng/mL) for all subjects following the 0.1 and 0.5 mg/kg doses. Ponezumab was quantified for 1 subject in the 1.0 mg/kg dose group at Month 3 (31.8 ng/mL) and 1 subject in the 1.0 mg/kg dose group at Month 19 (18.9 ng/mL). Ponezumab concentrations (mean ± standard deviation [SD]) for the 3.0 mg/kg dose group were 43.4±17.8 ng/mL (N=11) and 56.8±23.1 ng/mL (N=10) at Months 3 and 19, respectively. Finally, ponezumab concentrations (mean ± SD) for the 8.5 mg/kg dose group were 157.4±85.2 ng/mL (N=10) and 115.4±79.2 ng/mL (N=6) at Months 3 and 19, respectively. These CSF concentrations represent <1.0% of the mean plasma ponezumab concentrations at each corresponding dose.

Change From Baseline on the ADAS-cog Total Scores at Month 19: A summary of the MMRM inferential analysis of ADAS-cog total score change from Baseline is provided in Table 5.

For Part A, LS mean changes from Baseline to Day 570 in ADAS-cog were 8.36, 9.00, 9.25, and 6.98 for ponezumab 0.1 mg/kg, 0.5 mg/kg, 1.0 mg/kg and placebo Part A respectively. The differences in LS means compared with placebo Part A were 1.38, 2.02 and 2.27 for ponezumab 0.1 mg/kg, 0.5 mg/kg, 1.0 mg/kg respectively. All point estimates for the differences in LS means favored placebo Part A; however, all had 90% CIs that overlapped zero (0).

For Part B, the LS mean changes from Baseline to Day 570 in ADAS-cog were 9.58, 8.71 and 7.85 for ponezumab 3.0 mg/kg, 8.5 mg/kg and placebo Part B respectively. The differences in LS means compared with placebo Part B were 1.73 and 0.85 for ponezumab 3.0 mg/kg, 8.5 mg/kg respectively. All point estimates for the differences in LS means favored placebo Part B; however, all had 90% CIs that overlapped 0.

Table 5. MMRM Inferential Analysis of ADAS-cog Total Score Change From Baseline to Day 570

	Ponezumab 0.1 mg/kg	Ponezumab 0.5 mg/kg	Ponezumab 1.0 mg/kg	Placebo Part A	Ponezumab 3.0 mg/kg	Ponezumab 8.5 mg/kg	Placebo Part B
Day 570							
N	22	18	16	18	21	21	27
LS mean (SE)	8.36 (2.07)	9.00 (2.20)	9.25 (2.20)	6.98 (2.22)	9.58 (1.95)	8.71 (1.99)	7.85 (1.81)
Difference from placebo	1.38	2.02	2.27		1.73	0.85	
90% CI	-3.68, 6.45	-3.20, 7.23	-2.94, 7.48		-2.71, 6.17	-3.65, 5.35	
p-Value	0.6504	0.5213	0.4698		0.5183	0.7529	

Mixed Model Repeated Measures used terms for treatment, visit, baseline value, country, and treatment-by-visit interaction, with unstructured covariance matrix.
Negative differences from placebo favor ponezumab.
ADAS-cog = Alzheimer's Disease Assessment Scale-Cognitive Subscale; CI = confidence interval; LS = least squares; MMRM = Mixed Model Repeated Measures; N = number of subjects; SE = standard error.

Change From Baseline on the DAD Total Scores at Month 19: A summary of the MMRM inferential analysis of DAD total score change from Baseline is provided in Table 6.

For Part A, the LS mean changes from Baseline to Day 570 in DAD were -20.09, -16.20, -15.18, and-16.20 for ponezumab 0.1 mg/kg, 0.5 mg/kg, 1.0 mg/kg and placebo Part A respectively. The differences in LS means compared with placebo Part A at Day 570 were -4.07, -0.18, and 0.84 for ponezumab 0.1 mg/kg, 0.5 mg/kg, 1.0 mg/kg respectively. The point estimate for the difference in LS means for the 1.0 mg/kg dose level favored ponezumab; however, all point estimates for the differences in LS means had 90% CIs that overlapped 0.

For Part B, the LS mean changes from Baseline to Day 570 in DAD were -22.53, -18.12 and -18.44 for ponezumab 3.0 mg/kg, 8.5 mg/kg and placebo Part B respectively. The differences in LS means compared with placebo Part B at Day 570 were -4.09 and 0.32 for ponezumab 3.0 mg/kg, 8.5 mg/kg respectively. The point estimate for the difference in LS means for the 8.5 mg/kg dose level favored ponezumab; however, all point estimates for the differences in LS means had 90% CIs that overlapped zero (0).

Table 6. MMRM Inferential Analysis of DAD Total Score Change From Baseline to Day 570

	Ponezumab 0.1 mg/kg	Ponezumab 0.5 mg/kg	Ponezumab 1.0 mg/kg	Placebo Part A	Ponezumab 3.0 mg/kg	Ponezumab 8.5 mg/kg	Placebo Part B
Day 570							
N	21	21	18	18	24	22	27
LS mean (SE)	-20.09 (3.80)	-16.20 (3.90)	-15.18 (3.91)	-16.20 (4.07)	-22.53 (4.17)	-18.12 (4.30)	-18.44 (4.00)
Difference from placebo	-4.07	-0.18	0.84		-4.09	0.32	
90% CI	-13.38, 5.24	-9.59, 9.22	-8.57, 10.25		-13.77, 5.58	-9.48, 10.13	
p-Value	0.4688	0.9743	0.8824		0.4831	0.9562	

Mixed Model Repeated Measures used terms for treatment, visit, baseline value, country, and treatment-by-visit interaction, with unstructured covariance matrix.
Positive differences from placebo favor ponezumab.
CI = confidence interval; DAD = Disability Assessment for Dementia; LS = least squares; MMRM = Mixed Model Repeated Measures; N = number of subjects; SE = standard error.

Plasma and CSF Concentrations of Aβ Species: Both plasma Aβ1-x and Aβ1-40 exhibited dose-dependent increases in mean exposure. Plasma Aβ1-42 concentrations were sporadic and below the LLOQ (20 pg/mL) for the majority of subjects. The approximate mean increases from Baseline (predose) for plasma Aβ1-x (calculated as $C_{end, inf}$, Month 18/predose, Month 0) were 17.8-, 64.7-, 60.6-, 79.6-, and 208-fold following the 0.1, 0.5, 1.0, 3.0, and 8.5 mg/kg ponezumab doses, respectively. Plasma Aβ1-40 exhibited similar increases from Baseline over the dose range.

CSF concentrations of tau and p-tau: No clear dose-response was observed at Month 3 or Month 19 for any of the collected CSF biomarkers (Aβ1-x, Aβ1-40, Aβ1-42, tau, and p-tau), and these biomarkers appeared to display similar time courses for both the placebo- and PF-04360365-treated subjects. Additionally, it should be noted that the percent change-from Baseline data for each biomarker in each dose group were highly variable, with most coefficients of variation >100%.

Safety Results: A summary of the incidence of all causality non serious treatment-emergent AEs (TEAEs) occurring in at least 5% of subjects in any treatment group is provided in Table 7.

Table 7. Treatment-Emergent Non-Serious Adverse Events for Events Having a Frequency Rate ≥5% by System Organ Class and Preferred Term (All Causalities)

Number (%) of Subjects With Adverse Events by: System Organ Class and MedDRA (v 14.0) Preferred Term	Treatment						
	Ponezumab 0.1 mg/kg	Ponezumab 0.5 mg/kg	Ponezumab 1.0 mg/kg	Placebo Part A	Ponezumab 3.0 mg/kg	Ponezumab 8.5 mg/kg	Placebo Part B
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Evaluable for adverse events	25	25	25	24	32	31	32
With adverse events	24 (96.0)	24 (96.0)	23 (92.0)	24 (100.0)	26 (81.3)	28 (90.3)	32 (100.0)
Blood and lymphatic system disorders	2 (8.0)	4 (16.0)	1 (4.0)	0	1 (3.1)	2 (6.5)	4 (12.5)
Anaemia	2 (8.0)	3 (12.0)	0	0	0	1 (3.2)	4 (12.5)
Cardiac disorders	2 (8.0)	3 (12.0)	4 (16.0)	2 (8.3)	4 (12.5)	3 (9.7)	1 (3.1)
Atrial fibrillation	2 (8.0)	0	0	0	2 (6.3)	1 (3.2)	0
Coronary artery disease	0	0	0	0	2 (6.3)	1 (3.2)	0
Sinus bradycardia	0	0	2 (8.0)	0	0	1 (3.2)	0
Ventricular extrasystoles	0	2 (8.0)	0	0	0	0	0
Gastrointestinal disorders	12 (48.0)	11 (44.0)	9 (36.0)	4 (16.7)	8 (25.0)	13 (41.9)	9 (28.1)
Abdominal pain	0	2 (8.0)	2 (8.0)	1 (4.2)	1 (3.1)	2 (6.5)	1 (3.1)
Constipation	3 (12.0)	2 (8.0)	2 (8.0)	0	3 (9.4)	3 (9.7)	1 (3.1)
Diarrhoea	3 (12.0)	3 (12.0)	5 (20.0)	1 (4.2)	2 (6.3)	1 (3.2)	5 (15.6)
Faecal incontinence	2 (8.0)	2 (8.0)	0	1 (4.2)	0	3 (9.7)	1 (3.1)
Gastrooesophageal reflux disease	0	0	0	0	0	2 (6.5)	0
Nausea	3 (12.0)	4 (16.0)	1 (4.0)	1 (4.2)	4 (12.5)	3 (9.7)	1 (3.1)
Vomiting	3 (12.0)	4 (16.0)	1 (4.0)	0	0	0	3 (9.4)
General disorders and administration site conditions	5 (20.0)	8 (32.0)	9 (36.0)	6 (25.0)	7 (21.9)	7 (22.6)	4 (12.5)
Asthenia	0	2 (8.0)	2 (8.0)	0	0	0	0
Chest discomfort	0	2 (8.0)	1 (4.0)	0	0	0	0
Chest pain	1 (4.0)	0	1 (4.0)	0	1 (3.1)	2 (6.5)	0
Fatigue	4 (16.0)	3 (12.0)	5 (20.0)	1 (4.2)	4 (12.5)	4 (12.9)	3 (9.4)
Irritability	1 (4.0)	2 (8.0)	0	3 (12.5)	0	2 (6.5)	0
Infections and infestations	13 (52.0)	12 (48.0)	13 (52.0)	14 (58.3)	13 (40.6)	7 (22.6)	18 (56.3)
Bronchitis	0	1 (4.0)	2 (8.0)	1 (4.2)	0	0	2 (6.3)
Cystitis	0	0	2 (8.0)	2 (8.3)	0	0	0
Gastroenteritis	0	0	1 (4.0)	1 (4.2)	1 (3.1)	0	2 (6.3)
Herpes zoster	0	2 (8.0)	1 (4.0)	0	0	0	0

Table 7. Treatment-Emergent Non-Serious Adverse Events for Events Having a Frequency Rate ≥5% by System Organ Class and Preferred Term (All Causalities)

Number (%) of Subjects With Adverse Events by: System Organ Class and MedDRA (v 14.0) Preferred Term	Treatment						
	Ponezumab 0.1 mg/kg	Ponezumab 0.5 mg/kg	Ponezumab 1.0 mg/kg	Placebo Part A	Ponezumab 3.0 mg/kg	Ponezumab 8.5 mg/kg	Placebo Part B
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Influenza	0	0	2 (8.0)	0	1 (3.1)	1 (3.2)	0
Nasopharyngitis	4 (16.0)	0	2 (8.0)	1 (4.2)	5 (15.6)	3 (9.7)	4 (12.5)
Onychomycosis	0	2 (8.0)	0	0	0	0	1 (3.1)
Pneumonia	0	0	3 (12.0)	0	1 (3.1)	1 (3.2)	2 (6.3)
Tooth abscess	1 (4.0)	0	0	1 (4.2)	0	0	2 (6.3)
Upper respiratory tract infection	5 (20.0)	4 (16.0)	5 (20.0)	7 (29.2)	1 (3.1)	2 (6.5)	1 (3.1)
Urinary tract infection	4 (16.0)	3 (12.0)	2 (8.0)	3 (12.5)	4 (12.5)	2 (6.5)	2 (6.3)
Injury, poisoning and procedural complications	7 (28.0)	10 (40.0)	7 (28.0)	5 (20.8)	12 (37.5)	9 (29.0)	12 (37.5)
Contusion	1 (4.0)	4 (16.0)	1 (4.0)	2 (8.3)	6 (18.8)	2 (6.5)	5 (15.6)
Fall	2 (8.0)	3 (12.0)	3 (12.0)	3 (12.5)	8 (25.0)	4 (12.9)	9 (28.1)
Joint sprain	1 (4.0)	1 (4.0)	0	3 (12.5)	0	1 (3.2)	1 (3.1)
Laceration	1 (4.0)	1 (4.0)	1 (4.0)	0	4 (12.5)	0	1 (3.1)
Periorbital haematoma	0	1 (4.0)	1 (4.0)	0	0	0	2 (6.3)
Investigations	8 (32.0)	7 (28.0)	8 (32.0)	6 (25.0)	9 (28.1)	10 (32.3)	7 (21.9)
Blood glucose increased	0	0	0	1 (4.2)	2 (6.3)	2 (6.5)	1 (3.1)
Cardiac murmur	0	0	0	0	0	0	2 (6.3)
Electrocardiogram T wave inversion	0	2 (8.0)	0	0	0	0	0
Weight decreased	2 (8.0)	3 (12.0)	4 (16.0)	1 (4.2)	2 (6.3)	3 (9.7)	1 (3.1)
Weight increased	4 (16.0)	2 (8.0)	1 (4.0)	2 (8.3)	2 (6.3)	0	0
Metabolism and nutrition disorders	4 (16.0)	4 (16.0)	2 (8.0)	3 (12.5)	5 (15.6)	5 (16.1)	6 (18.8)
Decreased appetite	0	1 (4.0)	2 (8.0)	0	1 (3.1)	4 (12.9)	2 (6.3)
Vitamin D deficiency	1 (4.0)	1 (4.0)	0	2 (8.3)	0	0	0
Musculoskeletal and connective tissue disorders	9 (36.0)	8 (32.0)	8 (32.0)	7 (29.2)	12 (37.5)	6 (19.4)	13 (40.6)
Arthralgia	0	2 (8.0)	2 (8.0)	1 (4.2)	3 (9.4)	1 (3.2)	3 (9.4)
Back pain	2 (8.0)	2 (8.0)	4 (16.0)	1 (4.2)	3 (9.4)	2 (6.5)	4 (12.5)
Muscle spasms	2 (8.0)	0	1 (4.0)	1 (4.2)	1 (3.1)	0	0
Muscular weakness	0	0	1 (4.0)	2 (8.3)	0	0	1 (3.1)
Musculoskeletal pain	2 (8.0)	0	0	1 (4.2)	0	1 (3.2)	2 (6.3)

Table 7. Treatment-Emergent Non-Serious Adverse Events for Events Having a Frequency Rate ≥5% by System Organ Class and Preferred Term (All Causalities)

Number (%) of Subjects With Adverse Events by: System Organ Class and MedDRA (v 14.0) Preferred Term	Treatment						
	Ponezumab 0.1 mg/kg	Ponezumab 0.5 mg/kg	Ponezumab 1.0 mg/kg	Placebo Part A	Ponezumab 3.0 mg/kg	Ponezumab 8.5 mg/kg	Placebo Part B
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Neck pain	0	1 (4.0)	2 (8.0)	0	1 (3.1)	0	1 (3.1)
Pain in extremity	2 (8.0)	1 (4.0)	2 (8.0)	1 (4.2)	1 (3.1)	0	2 (6.3)
Neoplasms benign, malignant and unspecified (inclusive cysts and polyps)	0	1 (4.0)	2 (8.0)	4 (16.7)	2 (6.3)	3 (9.7)	2 (6.3)
Basal cell carcinoma	0	0	0	3 (12.5)	0	1 (3.2)	1 (3.1)
Nervous system disorders	16 (64.0)	14 (56.0)	8 (32.0)	15 (62.5)	16 (50.0)	12 (38.7)	21 (65.6)
Cerebellar microhaemorrhage	1 (4.0)	0	1 (4.0)	2 (8.3)	0	1 (3.2)	0
Cerebral microhaemorrhage	4 (16.0)	6 (24.0)	1 (4.0)	6 (25.0)	2 (6.3)	6 (19.4)	5 (15.6)
Dizziness	2 (8.0)	2 (8.0)	1 (4.0)	3 (12.5)	3 (9.4)	1 (3.2)	3 (9.4)
Dizziness postural	0	0	2 (8.0)	0	0	1 (3.2)	1 (3.1)
Headache	4 (16.0)	3 (12.0)	1 (4.0)	4 (16.7)	6 (18.8)	5 (16.1)	8 (25.0)
Intention tremor	0	1 (4.0)	1 (4.0)	0	1 (3.1)	2 (6.5)	0
Parkinsonism	2 (8.0)	0	0	0	0	0	0
Somnolence	1 (4.0)	0	0	0	0	1 (3.2)	2 (6.3)
Syncope	1 (4.0)	0	0	1 (4.2)	2 (6.3)	0	1 (3.1)
Tremor	2 (8.0)	1 (4.0)	0	0	1 (3.1)	2 (6.5)	0
Psychiatric disorders	10 (40.0)	11 (44.0)	12 (48.0)	9 (37.5)	12 (37.5)	13 (41.9)	12 (37.5)
Aggression	2 (8.0)	2 (8.0)	1 (4.0)	1 (4.2)	1 (3.1)	1 (3.2)	0
Agitation	1 (4.0)	4 (16.0)	3 (12.0)	3 (12.5)	2 (6.3)	4 (12.9)	2 (6.3)
Anxiety	3 (12.0)	5 (20.0)	1 (4.0)	3 (12.5)	3 (9.4)	3 (9.7)	2 (6.3)
Confusional state	0	0	2 (8.0)	1 (4.2)	3 (9.4)	6 (19.4)	2 (6.3)
Delirium	0	0	2 (8.0)	0	0	0	0
Delusion	0	1 (4.0)	2 (8.0)	1 (4.2)	0	1 (3.2)	2 (6.3)
Depressed mood	0	0	2 (8.0)	0	1 (3.1)	0	0
Depression	2 (8.0)	0	4 (16.0)	0	0	2 (6.5)	3 (9.4)
Depressive symptom	0	0	0	0	1 (3.1)	0	2 (6.3)
Disorientation	0	0	1 (4.0)	0	1 (3.1)	2 (6.5)	0
Insomnia	0	1 (4.0)	1 (4.0)	3 (12.5)	4 (12.5)	2 (6.5)	0

Table 7. Treatment-Emergent Non-Serious Adverse Events for Events Having a Frequency Rate ≥5% by System Organ Class and Preferred Term (All Causalities)

Number (%) of Subjects With Adverse Events by: System Organ Class and MedDRA (v 14.0) Preferred Term	Treatment						
	Ponezumab 0.1 mg/kg	Ponezumab 0.5 mg/kg	Ponezumab 1.0 mg/kg	Placebo Part A	Ponezumab 3.0 mg/kg	Ponezumab 8.5 mg/kg	Placebo Part B
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Paranoia	2 (8.0)	0	0	1 (4.2)	0	0	0
Renal and urinary disorders	7 (28.0)	3 (12.0)	5 (20.0)	3 (12.5)	2 (6.3)	8 (25.8)	3 (9.4)
Haematuria	2 (8.0)	0	2 (8.0)	0	1 (3.1)	2 (6.5)	1 (3.1)
Pollakiuria	2 (8.0)	0	1 (4.0)	1 (4.2)	0	2 (6.5)	0
Urinary incontinence	2 (8.0)	2 (8.0)	1 (4.0)	1 (4.2)	1 (3.1)	2 (6.5)	1 (3.1)
Urinary retention	0	0	2 (8.0)	0	0	0	0
Reproductive system and breast disorders	1 (4.0)	2 (8.0)	5 (20.0)	3 (12.5)	2 (6.3)	3 (9.7)	0
Benign prostatic hyperplasia	0	2 (8.0)	4 (16.0)	0	0	0	0
Respiratory, thoracic and mediastinal disorders	6 (24.0)	4 (16.0)	10 (40.0)	5 (20.8)	6 (18.8)	2 (6.5)	4 (12.5)
Cough	2 (8.0)	2 (8.0)	8 (32.0)	4 (16.7)	3 (9.4)	1 (3.2)	1 (3.1)
Dyspnoea	0	0	1 (4.0)	0	2 (6.3)	0	1 (3.1)
Dyspnoea exertional	2 (8.0)	1 (4.0)	0	0	1 (3.1)	0	0
Rhinorrhoea	2 (8.0)	0	1 (4.0)	1 (4.2)	0	0	0
Skin and subcutaneous tissue disorders	7 (28.0)	4 (16.0)	10 (40.0)	8 (33.3)	5 (15.6)	7 (22.6)	8 (25.0)
Erythema	1 (4.0)	0	1 (4.0)	1 (4.2)	2 (6.3)	0	0
Pruritus	2 (8.0)	0	0	0	1 (3.1)	0	1 (3.1)
Rash	4 (16.0)	0	1 (4.0)	1 (4.2)	1 (3.1)	1 (3.2)	2 (6.3)
Skin lesion	0	1 (4.0)	2 (8.0)	1 (4.2)	0	2 (6.5)	2 (6.3)
Vascular disorders	6 (24.0)	6 (24.0)	2 (8.0)	1 (4.2)	7 (21.9)	2 (6.5)	6 (18.8)
Flushing	0	0	0	0	2 (6.3)	1 (3.2)	2 (6.3)
Hypertension	4 (16.0)	3 (12.0)	0	1 (4.2)	4 (12.5)	1 (3.2)	2 (6.3)

Subjects were only counted once per treatment for each row.
Includes data up to 999 days after last dose of study drug.
MedDRA (v14.0) coding dictionary applied.
MedDRA = Medical Dictionary for Regulatory Activities; n = number of subjects; v = version.

A summary of the incidence of treatment-related TEAEs occurring in at least 5% of subjects in any treatment group is provided in Table 8.

The most commonly occurring treatment-related TEAEs were cerebral microhemorrhage (21 subjects), headache (11 subjects), and fatigue (9 subjects).

The most frequently reported treatment-related AEs for all Part A subjects during Part A of the study were cerebral microhemorrhage (12 subjects), headache (5 subjects), and fatigue (4 subjects).

The most frequently reported treatment-related AEs for all Part B subjects during Part B of the study were cerebral microhemorrhage (9 subjects), headache (6 subjects), fatigue (5 subjects), and flushing (5 subjects).

Table 8. Incidence of Treatment-Emergent Adverse Events Occurring in at Least 5% of Subjects in Any Treatment Group (Treatment-Related)

MedDRA (v14.0) Preferred Term	Ponezumab 0.1 mg/kg (N=25) n (%)	Ponezumab 0.5 mg/kg (N=25) n (%)	Ponezumab 1.0 mg/kg (N=25) n (%)	Placebo Part A (N=24) n (%)	Ponezumab 3.0 mg/kg (N=32) n (%)	Ponezumab 8.5 mg/kg (N=31) n (%)	Placebo Part B (N=32) n (%)
Cerebral microhemorrhage	3 (12.0)	4 (16.0)	1 (4.0)	4 (16.7)	1 (3.1)	3 (9.7)	5 (15.6)
Headache	4 (16.0)	0	0	1 (4.2)	2 (6.3)	1 (3.2)	3 (9.4)
Fatigue	1 (4.0)	0	3 (12.0)	0	1 (3.1)	2 (6.5)	2 (6.3)
Flushing	0	0	0	0	2 (6.3)	1 (3.2)	2 (6.3)
Dizziness	0	2 (8.0)	0	1 (4.2)	0	0	1 (3.1)
Diarrhea	1 (4.0)	0	0	0	0	0	2 (6.3)
Ventricular extrasystoles	0	2 (8.0)	0	0	0	0	0

Non SAE/SAE results are not separated out. Subjects were only counted once per treatment for each row.
Includes data on and after first date of dose (Day 1).
Includes data up to 999 days after last dose of drug.
MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects; n = number of subject with specified criteria; SAE = serious adverse event; v = version.

Serious Adverse Events (SAEs): Treatment-Emergent SAEs are presented in Table 9. A total of 45 subjects reported SAEs during this study including 3 subjects who had treatment-related SAEs (1 subject who received ponezumab 0.1 mg/kg developed subdural hygroma, 1 subject who received ponezumab 0.5 mg/kg developed vasogenic cerebral edema and hemosiderosis, and 1 subject who received placebo Part A developed prostate cancer).

Table 9. Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term (All Causalities)

Number (%) of Subjects With Adverse Events by: System Organ Class MedDRA (v14.0) Preferred Term	Ponezumab 0.1 mg/kg n (%)	Ponezumab 0.5 mg/kg n (%)	Ponezumab 1.0 mg/kg n (%)	Placebo Part A n (%)	Ponezumab 3.0 mg/kg n (%)	Ponezumab 8.5 mg/kg n (%)	Placebo Part B n (%)
Evaluable for AEs	25	25	25	24	32	31	32
With AEs	7 (28.0)	8 (32.0)	7 (28.0)	3 (12.5)	7 (21.9)	10 (32.3)	3 (9.4)
Blood and lymphatic system disorders	0	0	1 (4.0)	0	0	0	0
Anaemia	0	0	1 (4.0)	0	0	0	0
Cardiac disorders	1 (4.0)	2 (8.0)	1 (4.0)	0	2 (6.3)	1 (3.2)	1 (3.1)
Acute coronary syndrome	0	0	0	0	0	0	1 (3.1)
Acute myocardial infarction	0	0	0	0	0	0	1 (3.1)
Angina pectoris	0	0	1 (4.0)	0	0	0	0
Atrial fibrillation	1 (4.0)	1 (4.0)	0	0	0	0	0
Bradycardia	0	1 (4.0)	0	0	0	0	0
Cardiogenic shock	0	0	0	0	1 (3.1)	0	0
Coronary artery stenosis	0	0	0	0	1 (3.1)	0	0
Myocardial infarction	0	0	0	0	2 (6.3)	0	0
Myocardial ischaemia	0	0	0	0	0	1 (3.2)	0
Sick sinus syndrome	0	0	0	0	0	1 (3.2)	0
Ear and labyrinth disorders	0	0	0	0	1 (3.1)	0	0
Vertigo positional	0	0	0	0	1 (3.1)	0	0
Gastrointestinal disorders	0	0	1 (4.0)	1 (4.2)	1 (3.1)	1 (3.2)	1 (3.1)
Colonic polyp	0	0	1 (4.0)	0	0	0	0
Dyspepsia	0	0	0	0	0	1 (3.2)	0
Gastrooesophageal reflux disease	0	0	0	0	0	1 (3.2)	0
Haemorrhoids	0	0	0	0	0	0	1 (3.1)
Periodontitis	0	0	0	0	1 (3.1)	0	0
Rectal haemorrhage	0	0	0	1 (4.2)	0	0	0
General disorders and administration site conditions	0	1 (4.0)	0	0	1 (3.1)	0	0
Chest discomfort	0	1 (4.0)	0	0	0	0	0
Pyrexia	0	0	0	0	1 (3.1)	0	0
Hepatobiliary disorders	0	1 (4.0)	0	0	0	0	0
Cholecystitis acute	0	1 (4.0)	0	0	0	0	0
Infections and infestations	1 (4.0)	1 (4.0)	1 (4.0)	1 (4.2)	0	0	0
Cellulitis	1 (4.0)	0	1 (4.0)	0	0	0	0
Pneumonia	0	1 (4.0)	0	1 (4.2)	0	0	0
Injury, poisoning and procedural complications	1 (4.0)	2 (8.0)	2 (8.0)	0	1 (3.1)	4 (12.9)	1 (3.1)
Fall	0	0	1 (4.0)	0	1 (3.1)	1 (3.2)	0

Table 9. Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term (All Causalities)

Number (%) of Subjects With Adverse Events by: System Organ Class MedDRA (v14.0) Preferred Term	Ponezumab 0.1 mg/kg n (%)	Ponezumab 0.5 mg/kg n (%)	Ponezumab 1.0 mg/kg n (%)	Placebo Part A n (%)	Ponezumab 3.0 mg/kg n (%)	Ponezumab 8.5 mg/kg n (%)	Placebo Part B n (%)
Hip fracture	0	0	1 (4.0)	0	0	1 (3.2)	0
Humerus fracture	0	0	1 (4.0)	0	1 (3.1)	0	0
Incisional hernia	0	0	0	0	0	0	1 (3.1)
Joint dislocation	0	0	1 (4.0)	0	0	0	0
Medication error	1 (4.0)	0	0	0	0	0	0
Muscle rupture	0	0	0	0	0	1 (3.2)	0
Rib fracture	0	1 (4.0)	0	0	0	0	0
Road traffic accident	0	1 (4.0)	0	0	0	0	0
Skull fracture	0	1 (4.0)	0	0	0	0	0
Spinal compression fracture	0	0	0	0	0	1 (3.2)	0
Subdural haematoma	0	1 (4.0)	0	0	0	0	0
Wrong drug administered	0	0	0	0	0	1 (3.2)	0
Metabolism and nutrition disorders	1 (4.0)	1 (4.0)	0	0	0	0	0
Haemosiderosis	0	1 (4.0)	0	0	0	0	0
Hypoglycaemia	1 (4.0)	0	0	0	0	0	0
Musculoskeletal and connective tissue disorders	0	0	0	0	1 (3.1)	1 (3.2)	0
Arthritis	0	0	0	0	1 (3.1)	0	0
Bursitis	0	0	0	0	0	1 (3.2)	0
Periarthritis	0	0	0	0	0	1 (3.2)	0
Rotator cuff syndrome	0	0	0	0	0	1 (3.2)	0
Neoplasms benign, malignant and unspecified (including cysts and polyps)	1 (4.0)	1 (4.0)	0	2 (8.3)	0	2 (6.5)	0
Breast cancer in situ	0	0	0	0	0	1 (3.2)	0
Colon adenoma	0	0	0	0	0	1 (3.2)	0
Ovarian neoplasm	0	1 (4.0)	0	0	0	0	0
Prostate cancer	0	0	0	2 (8.3)	0	0	0
Squamous cell carcinoma	1 (4.0)	0	0	0	0	0	0
Nervous system disorders	3 (12.0)	3 (12.0)	1 (4.0)	0	1 (3.1)	3 (9.7)	2 (6.3)
Altered state of consciousness	0	0	0	0	0	1 (3.2)	0
Cerebral haemorrhage	0	1 (4.0)	0	0	0	0	0
Cerebral ischaemia	0	0	0	0	0	1 (3.2)	0
Convulsion	1 (4.0)	1 (4.0)	0	0	0	0	0
Dementia Alzheimer's type	0	0	0	0	0	1 (3.2)	0
Guillain-Barre syndrome	1 (4.0)	0	0	0	0	0	0

Table 9. Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term (All Causalities)

Number (%) of Subjects With Adverse Events by: System Organ Class MedDRA (v14.0) Preferred Term	Ponezumab 0.1 mg/kg n (%)	Ponezumab 0.5 mg/kg n (%)	Ponezumab 1.0 mg/kg n (%)	Placebo Part A n (%)	Ponezumab 3.0 mg/kg n (%)	Ponezumab 8.5 mg/kg n (%)	Placebo Part B n (%)
Haemorrhage intracranial	0	0	0	0	0	0	1 (3.1)
Meningeal disorder	1 (4.0)	0	0	0	0	0	0
Presyncope	0	0	1 (4.0)	0	0	0	0
Subdural hygroma	1 (4.0)	0	0	0	0	1 (3.2)	0
Syncope	0	1 (4.0)	0	0	1 (3.1)	0	0
Transient ischaemic attack	0	0	0	0	0	0	1 (3.1)
Vasogenic cerebral oedema	0	1 (4.0)	0	0	0	0	0
Psychiatric disorders	1 (4.0)	1 (4.0)	3 (12.0)	0	0	0	0
Aggression	1 (4.0)	0	0	0	0	0	0
Agitation	0	0	1 (4.0)	0	0	0	0
Delirium	0	1 (4.0)	2 (8.0)	0	0	0	0
Renal and urinary disorders	0	1 (4.0)	0	0	0	0	0
Nephrolithiasis	0	1 (4.0)	0	0	0	0	0
Reproductive system and breast disorders	1 (4.0)	1 (4.0)	0	0	0	1 (3.2)	0
Benign prostatic hyperplasia	1 (4.0)	1 (4.0)	0	0	0	0	0
Fibrocystic breast disease	0	0	0	0	0	1 (3.2)	0
Respiratory, thoracic and mediastinal disorders	1 (4.0)	1 (4.0)	0	0	1 (3.1)	1 (3.2)	0
Acute pulmonary oedema	0	0	0	0	1 (3.1)	0	0
Epistaxis	0	0	0	0	1 (3.1)	0	0
Haemothorax	0	1 (4.0)	0	0	0	0	0
Pleural effusion	1 (4.0)	0	0	0	0	0	0
Pulmonary embolism	1 (4.0)	0	0	0	0	1 (3.2)	0

Subjects were only counted once per treatment for each row.
Included data up to 999 days after last dose of study drug.
MedDRA (v14.0) coding dictionary applied.
MedDRA = Medical Dictionary for Regulatory Activities; n = number of subjects with specified criteria; v = version.

Permanent Discontinuations due to AEs: A total of 10 subjects discontinued from treatment, but continued study participation, due to AEs. These subjects remained in the study (Table 10).

Table 10. Discontinuations From Treatment due to Adverse Events

Subject Serial Number	MedDRA (v14.0) Preferred Term	Study Start Day/Stop Day[a]	Time Postdose (Days)	Duration	Severity/ Outcome	Causality
Ponezumab 0.1 mg/kg						
1	Rash	248/477	8.90	[229.67]	Moderate/ resolved	Study drug
2	Cerebral microhemorrhage	387/>716	23.10	[>329.46]	Mild/ still present	Study drug
Ponezumab 1.0 mg/kg						
3	Delirium	506/508	[20.61]	[3.00]	Severe/ resolved	Other illness
4	Colonic polyp	482/554	54.99	72.24	Mild/Resolved	Other illness
Placebo Part A						
5	Cerebral microhemorrhage	387/[>543]	[33.61]	[>157.00]	Mild/ still present	Disease under study
Ponezumab 3.0 mg/kg						
6	Myocardial infarction	511/515	89.08	4.00	Severe/ resolved	Other - unknown
7	Myocardial infarction	174/178	[53.58]	[5.00]	Moderate/ resolved	Other illness
Ponezumab 8.5 mg/kg						
8	Cerebral microhemorrhage	387/[>727]	20.13	[>340.48]	Mild/ still present	Disease under study
9	Rash	127/234	0.65	107.29	Moderate/ resolved	Study drug
10	Hepatic enzyme increased	214/287	24/11	72.78	Moderate/ resolved	Concomitant treatment

Included subjects with study drug action = permanently discontinued.
Age at Screening.
Values in brackets were imputed from incomplete dates and times.
MedDRA = Medical Dictionary for Regulatory Activities; v = version.
a. Day relative to start of treatment. First day of study treatment = Day 1.

Table 11 summarizes permanent discontinuations from the study due to AEs. One (1) subject discontinued from the study during the follow-up period due to an AE (road traffic accident; ponezumab 0.5 mg/kg).

Table 11. Discontinuations From Study due to Adverse Events

Subject Serial Number	MedDRA (v14.0) Preferred Term	Study Start Day/Stop Day[a]	Time Postdose (Days)	Duration	Severity/ Outcome	Causality
Ponezumab 0.5 mg/kg						
1	Road traffic accident	612/612	71.32	0.02	Severe/resolved	Other – car accident

Included subjects with study drug action = no action taken' and 'subject action'='D/C study'.
Age at Screening.
D/C = discontinued; MedDRA = Medical Dictionary for Regulatory Activities; v = version.
a. Day relative to start of treatment. First day of study treatment = Day 1.

A listing of permanent discontinuations from treatment and the study due to AEs is provided in Table 12. A total of 9 subjects discontinued from treatment and the study due to AEs. One (1) AE that led to discontinuation from the study and from study treatment was considered treatment-related (exertional dyspnea).

Table 12. Discontinuations From Treatment and Study due to Adverse Event

Subject Serial Number	MedDRA (v14.0) Preferred Term	Study Start Day/Stop Day[a]	Time Postdose (Days)	Duration	Severity/ Outcome	Causality
Ponezumab 0.5 mg/kg						
1	Ovarian neoplasm	310/[>330]	[14.60]	[>21.00]	Severe/ still present	Other illness
Ponezumab 1.0 mg/kg						
2	Anemia	404/613	[51.61]	[210.00]	Moderate/ resolved	Other illness
3	Hip fracture	401/403	49.43	1.95	Severe/ resolved	Other – fall
4	Aggression	286/[>425]	41.90	[>139.67]	Mild/ still present	Disease under study
Placebo Part A						
5	Rib fracture	462/[>478]	[39.62]	[>17.00]	Moderate/ still present	Other – fall
Ponezumab 3.0 mg/kg						
6	Dyspnea exertional	2/15	0.95	13.00	Mild/ resolved	Study drug
7	Humerus fracture	496/564	[12.60]	[69.00]	Moderate/ resolved	Other – accidental fall
Ponezumab 8.5 mg/kg						
8	Sick sinus syndrome	383/[>395]	[22.62]	[>13.00]	Moderate/ still present	Other – age related
Placebo Part B						
9	Hemorrhage intracranial	237/246	[66.61]	[9.14]	Severe/ resolved	Other illness
10	Acute coronary syndrome	360/363	[55.56]	[4.00]	Severe/ resolved	Other illness

Included subjects with study drug action = permanently discontinued and 'subject action' = 'D/C study'.
Age at Screening.
Values in brackets were imputed from incomplete dates and times.
D/C = discontinued; MedDRA = Medical Dictionary for Regulatory Activities; v = version.
a. Day relative to start of treatment. First day of study treatment = Day 1.

Dose Reductions or Temporary Discontinuations due to AEs: A total of 13 subjects had a temporary discontinuation of study drug due to an AE (1 ponezumab 0.1 mg/kg; 2 ponezumab 0.5 mg/kg; 1 ponezumab 1.0 mg/kg; 1 placebo Part A; 3 ponezumab 3.0 mg/kg; 1 ponezumab 8.5 mg/kg; and 4 placebo Part B subjects). There were no dose reductions due to AEs.

Deaths: Two (2) subjects died during the active treatment phase (2 placebo Part B subjects) and 1 subject died during the post-treatment follow-up phase (ponezumab 0.5 mg/kg). Reasons for death were road traffic accident (ponezumab 0.5 mg/kg), intracranial hemorrhage (placebo Part B), and acute coronary syndrome (placebo Part B). None of the deaths were considered related to ponezumab. Table 13 provides a summary of deaths.

Table 13. Summary of Deaths

Subject	MedDRA (v14.0) Preferred Term	Study Start Day/Stop Day[a]	Time Postdose (Days)	Duration (Days)	Severity/ Outcome	Causality
ponezumab 0.5 mg/kg						
1	Road traffic accident	612/612	71.32	0.02	Severe/resolved	Other – car accident
Placebo Part B						
2	Hemorrhage intracranial	237/246	[66.61]	[9.14]	Severe/resolved	Other illness
3	Acute coronary syndrome	360/363	[55.56]	[4.00]	Severe/resolved	Other illness

Age at Screening.
Values in brackets were imputed from incomplete dates and times.
MedDRA = Medical Dictionary for Regulatory Activities; v = version.
a. Day relative to start of treatment. First day of study treatment = Day 1.

Physical Examinations and Neurological Examinations: Clinician review of the physical evaluations across all study sites did not reveal any patterns of change between Screening and Last subject Visit that the Investigator deemed to be clinically significant. A summary of physical examination findings at Last Visit is provided in Table 14.

Clinician review of the neurological evaluations across all study sites did not reveal any patterns of change between Screening and Last subject Visit that the Investigator deemed to be clinically significant. A summary of neurological examination findings at Last Visit is provided in Table 15.

Table 14. Physical Examination Findings at Last Visit

Number of Subjects	Ponezumab 0.1 mg/kg		Ponezumab 0.5 mg/kg		Ponezumab 1.0 mg/kg		Placebo Part A		Ponezumab 3.0 mg/kg		Ponezumab 8.5 mg/kg		Placebo Part B	
	25		25		25		24		32		31		32	
Site	**NE**	**Abn**	**NE**	**Abn**	**NE**	**Abn**	**NE**	**Abn**	**NE**	**Abn**	**NE**	**Abn**	**NE**	**Abn**
Abdomen	23	1	20	1	21	0	20	0	30	1	26	3	26	0
Ears	23	0	21	0	21	0	20	1	31	1	26	1	27	1
Extremities	23	2	21	2	21	1	20	0	31	1	27	3	27	0
Eyes	23	2	21	2	21	1	20	0	31	0	27	0	27	2
General	23	1	21	1	21	1	20	0	31	0	27	0	27	0
Head	23	0	21	1	21	0	20	0	31	0	27	0	27	1
Heart	23	0	21	0	21	0	20	0	31	2	27	2	27	0
Lungs	23	0	20	0	21	0	20	1	31	0	27	1	27	0
Lymph nodes	23	0	21	0	21	0	20	0	31	0	27	0	27	0
Mouth	23	1	21	0	21	0	20	0	31	0	27	0	27	0
Musculoskeletal	23	2	21	0	21	1	20	2	31	1	27	3	27	4
Neck	23	0	21	0	21	1	20	0	31	0	27	0	27	0
Nose	23	2	21	0	21	0	20	0	31	0	27	0	27	0
Ocular fundi	22	1	21	1	21	0	18	0	31	0	26	0	23	0
Other	2	1	0	0	4	0	0	0	1	0	1	1	0	0
Pulses	23	0	21	0	21	0	20	0	31	0	27	0	27	0
Skin	23	3	21	1	21	1	20	3	31	5	27	3	27	4
Throat	23	0	21	0	21	0	20	0	31	0	27	0	27	0
Thyroid	23	0	21	0	21	0	20	0	31	0	27	0	27	0

Abn = Abnormal; NE = Number Examined.

Table 15. Neurological Examination Findings at Last Visit

Number of Subjects	Ponezumab 0.1 mg/kg		Ponezumab 0.5 mg/kg		Ponezumab 1.0 mg/kg		Placebo Part A		Ponezumab 3.0 mg/kg		Ponezumab 8.5 mg/kg		Placebo Part B	
	25		25		25		24		32		31		32	
Site	**NE**	**Abn**	**NE**	**Abn**	**NE**	**Abn**	**NE**	**Abn**	**NE**	**Abn**	**NE**	**Abn**	**NE**	**Abn**
Cerebellar function	25	1	25	0	25	0	24	0	32	0	31	0	32	0
Cranial nerve function	25	3	25	2	25	3	24	4	32	2	31	3	32	2
Mental state	25	1	25	2	25	3	24	2	32	2	31	1	32	3
Motor function	25	3	25	3	25	5	24	1	32	1	31	2	32	1
Reflexes	25	3	25	2	25	3	24	1	32	1	31	2	32	2
Sensory function	25	0	25	2	25	0	24	1	32	0	31	1	32	1

Abn = Abnormal; NE = Number Examined.

Vital Signs: A summary of categorical vital signs findings is provided in Table 16. Abnormalities in blood pressure and pulse rate were observed in subjects treated with ponezumab and placebo, with no clear differences between treatment groups.

Table 16. Summary of Categorical Vital Signs Findings

Parameter Criteria n (%)	Ponezumab 0.1 mg/kg (N=25)	Ponezumab 0.5 mg/kg (N=25)	Ponezumab 1.0 mg/kg (N=25)	Placebo Part A (N=24)	Ponezumab 3.0 mg/kg (N=32)	Ponezumab 8.5 mg/kg (N=31)	Placebo Part B (N=32)
Systolic blood pressure (mm Hg)							
<90	1 (4.0)	1 (4.0)	1 (4.0)	1 (4.2)	2 (6.3)	1 (3.2)	3 (9.4)
Increase from baseline ≥30	8 (32.0)	6 (24.0)	7 (28.0)	9 (37.5)	9 (28.1)	6 (19.4)	7 (21.9)
Decrease from baseline ≥30	10 (40.0)	10 (40.0)	11 (44.0)	8 (33.3)	13 (40.6)	10 (32.3)	11 (34.4)
Diastolic blood pressure (mm Hg)							
<50	0	5 (20.0)	4 (16.0)	4 (16.7)	2 (6.3)	8 (25.8)	11 (34.4)
Increase from baseline ≥20	6 (24.0)	8 (32.0)	9 (36.0)	4 (16.7)	12 (37.5)	9 (29.0)	6 (18.8)
Decrease from baseline ≥20	6 (24.0)	7 (28.0)	10 (40.0)	9 (37.5)	5 (15.6)	10 (32.3)	11 (34.4)
Pulse rate (bpm)							
<40	0	1 (4.0)	1 (4.0)	1 (4.2)	1 (3.1)	0	0
>120	0	0	0	0	1 (3.1)	0	0

Baseline was defined as the latest non-missing value from a range of pretreatment visits.
N = total number of subjects evaluated against the criteria; n = number of subjects who met that criteria; bpm = beats per minute.

Clinical Laboratory Values: Abnormalities in laboratory parameters (RBCs, WBCs, CSF and glucose) were observed in subjects treated with ponezumab and placebo, with no clear differences between treatment groups (Table 17). Median changes from Baseline were generally similar among treatment groups. Abnormalities in BP and pulse rate were observed in subjects treated with ponezumab and placebo, with no clear differences between treatment groups.

Table 17. Incidence of Laboratory Test Abnormalities (Abnormal Baseline)

					Ponezumab 0.1 mg/kg		Ponezumab 0.5 mg/kg		Ponezumab 1.0 mg/kg		Placebo Part A		Ponezumab 3.0 mg/kg		Ponezumab 8.5 mg/kg		Placebo Part B	
Number of Subjects Evaluable for Laboratory Abnormalities					**24**		**23**		**24**		**22**		**28**		**26**		**30**	
Number (%) With Laboratory Abnormalities					**11**		**6**		**9**		**14**		**11**		**10**		**14**	
Group	**Parameter**	**Units**	**Primary Criteria**	**Secondary Criteria**	**N**	**n**	**N**	**n**	**N**	**n**	**N**	**n**	**N**	**n**	**N**	**n**	**N**	**n**
Hematology	Hemoglobin	g/dl	<0.8 × LLN	<0.8 × baseline	3	0	2	0	2	0			3	0	2	0	3	1
	Hematocrit	%	<0.8 × LLN	<0.8 × baseline	2	0	1	0	1	0			2	0	2	0	3	1
	RBC count	$10^6/mm^3$	<0.8 × LLN	<0.8 × baseline	3	0	2	0	4	0	4	0	4	0	4	1	8	1
	Platelets	$10^3/mm^3$	<0.5 × LLN	<0.8 × baseline									1	0	1	0		
			>1.75 × ULN	>1.75 × baseline									1	0	1	0		
	WBC count	$10^3/mm^3$	>0.6 × ULN	>0.6 × baseline	3	0	2	0	1	0			4	0	2	0		
			>1.5 × ULN	>1.5 × baseline	3	1	2	0	1	0			4	0	2	0		
	Lymphocytes (Abs)	$10^3/mm^3$	<0.8 × LLN	<0.8 × baseline	1	0	1	0			1	0	1	0	3	1	1	0
			>1.2 × ULN	>1.2 × baseline	1	1	1	0			1	0	1	0	3	1	1	0
	Total neutrophils (Abs)	$10^3/mm^3$	<0.8 × LLN	<0.8 × baseline	2	0	2	0					4	1	1	0		
			>1.2 × ULN	>1.2 × baseline	2	1	2	0					4	1	1	0		
	Eosinophils (Abs)	$10^3/mm^3$	>1.2 × ULN	>1.2 × baseline													1	0
Coagulation	APTT	Sec	>1.1 × ULN	>1.1 × baseline	1	0									1	0		
	Prothrombin	Sec	>1.1 × ULN	>1.1 × baseline	1	0					1	1			1	0		
	Prothrombin international ratio		>1.1 × ULN	>1.1 × baseline													1	0
Liver function	Total bilirubin	mg/dL	>1.5 × ULN	>1.5 × baseline	1	0									1	0		
	Aspartate aminotransferase	IU/L	>3.0 × ULN	>1.5 × baseline	1	0			2	0			2	0	1	0	2	0

Table 17. Incidence of Laboratory Test Abnormalities (Abnormal Baseline)

					Ponezumab 0.1 mg/kg		Ponezumab 0.5 mg/kg		Ponezumab 1.0 mg/kg		Placebo Part A		Ponezumab 3.0 mg/kg		Ponezumab 8.5 mg/kg		Placebo Part B	
Number of Subjects Evaluable for Laboratory Abnormalities					**24**		**23**		**24**		**22**		**28**		**26**		**30**	
Number (%) With Laboratory Abnormalities					**11**		**6**		**9**		**14**		**11**		**10**		**14**	
Group	**Parameter**	**Units**	**Primary Criteria**	**Secondary Criteria**	**N**	**n**	**N**	**n**	**N**	**n**	**N**	**n**	**N**	**n**	**N**	**n**	**N**	**n**
	Alanine aminotransferase	IU/L	>3.0 × ULN	>1.5 × baseline			1	0	1	0					2	0	2	0
	Alkaline phosphatase	IU/L	>3.0 × ULN	>1.5 × baseline									2	0				
	Total protein	g/dL	<0.8 × LLN	<0.8 × baseline	1	0	3	0			3	0	1	0				
			>1.2 × ULN	>1.2 × baseline	1	0	3	0			3	0	1	0				
	Albumin	g/dL	<0.8 × LLN	<0.8 × baseline	1	0			1	0	2	0	1	0	1	0		
			>1.2 × ULN	>1.2 × baseline	1	0			1	0	2	0	1	0	1	0		
Renal function	Blood urea nitrogen	mg/dL	>1.3 × ULN	>1.3 × baseline			1	0	2	0							1	0
	Creatinine	mg/dL	>1.3 × ULN	>1.3 × baseline			1	1									1	0
	Creatinine clearance	mL/min	<0.6 × LLN	<0.6 × baseline	21	1	18	1	20	0	14	1	20	1	24	1	23	3
			>1.5 × ULN	>1.5 × baseline	21	0	18	0	20	0	14	0	20	0	24	0	23	0
	Uric acid	mg/dL	>1.2 × ULN	>1.2 × baseline									1	1			1	1
Electrolytes	Sodium	mEq/L	<0.95x LLN	<0.95x baseline	4	0	8	0	7	0	3	0	2	0	2	0	2	0
			>1.05 × ULN	>1.05 × baseline	4	2	8	0	7	0	3	0	2	0	2	0	2	0
	Potassium	mEq/L	<0.9 × LLN	<0.9 × baseline	1	0							4	0	1	0		
			>1.1 × ULN	>1.1 × baseline	1	0							4	0	1	0		
	Chloride	mEq/L	<0.9 × LLN	<0.9 × baseline	1	0												
			>1.1 × ULN	>1.1 × baseline	1	0												

Table 17. Incidence of Laboratory Test Abnormalities (Abnormal Baseline)

					Ponezumab 0.1 mg/kg		Ponezumab 0.5 mg/kg		Ponezumab 1.0 mg/kg		Placebo Part A		Ponezumab 3.0 mg/kg		Ponezumab 8.5 mg/kg		Placebo Part B	
Number of Subjects Evaluable for Laboratory Abnormalities					**24**		**23**		**24**		**22**		**28**		**26**		**30**	
Number (%) With Laboratory Abnormalities					**11**		**6**		**9**		**14**		**11**		**10**		**14**	
Group	**Parameter**	**Units**	**Primary Criteria**	**Secondary Criteria**	**N**	**n**	**N**	**n**	**N**	**n**	**N**	**n**	**N**	**n**	**N**	**n**	**N**	**n**
	Calcium	mg/dL	<0.9× LLN	<0.9× baseline	2	0			1	0	3	0	3	0				
			>1.1 × ULN	>1.1 × baseline	2	0			1	0	3	0	3	0				
	Bicarbonate (venous)	mEq/L	<0.9 × LLN	<0.75 × baseline							1	0	1	0			1	0
			>1.1 × ULN	>1.25 × baseline							1	0	1	0			1	0
Hormones	TSH	UIU/ML	<0.8 × LLN	<0.8 × baseline													1	0
			>1.2 × ULN	>1.2 × baseline													1	0
Clinical chemistry (other)	Glucose	mg/dL	<0.6 × LLN	<0.75 × baseline	8	0	1	0	7	0	6	0	10	0	7	0	10	0
			>1.5 × ULN	>1.25 × baseline	8	2	1	1	7	1	6	4	10	1	7	2	10	2
Immunology	Immunoglobulin G	g/L	<0.6 × LLN	<0.6 × baseline	1	0	1	0			2	0	1	0				
			>1.5 × ULN	>1.5 × baseline	1	0	1	0			2	0	1	0				
Urinalysis (dipstick)	Urine glucose (Qual)		≥1	≥1	1	1			1	1	1	1	2	1			1	0
	Urine blood/Hgb (Qual)		≥1	≥1			2	1							1	1		
Urinalysis (microscopy)	Urine RBC	/HPF	≥20	≥20									1	0			1	1
	Urine WBC	/HPF	≥20	≥20					1	1			1	0	1	0	2	2
	Urine crystals		≥1	≥1	5	5	3	3	8	8	10	10	5	5	4	4	7	7
Miscellaneous	CSF protein	mg/dL	<1.0 × LLN	<1.0 × baseline	1	0	1	0	1	0	3	0	3	0	3	0	4	0
			>1.0 × ULN	>1.0 × baseline	1	1	1	0	1	0	3	2	3	2	3	2	4	2

Table 17. Incidence of Laboratory Test Abnormalities (Abnormal Baseline)

					Ponezumab 0.1 mg/kg		Ponezumab 0.5 mg/kg		Ponezumab 1.0 mg/kg		Placebo Part A		Ponezumab 3.0 mg/kg		Ponezumab 8.5 mg/kg		Placebo Part B	
Number of Subjects Evaluable for Laboratory Abnormalities					**24**		**23**		**24**		**22**		**28**		**26**		**30**	
Number (%) With Laboratory Abnormalities					**11**		**6**		**9**		**14**		**11**		**10**		**14**	
Group	**Parameter**	**Units**	**Primary Criteria**	**Secondary Criteria**	**N**	**n**	**N**	**n**	**N**	**n**	**N**	**n**	**N**	**n**	**N**	**n**	**N**	**n**
	CSF glucose	mg/dL	<1.0 × LLN	<1.0 × baseline	1	0					1	0	1	0	4	0	2	0
			>1.0 × ULN	>1.0 × baseline	1	0					1	0	1	1	4	0	2	1
	CSF WBC	10^6/L	<1.0 × LLN	<1.0 × baseline													2	0
			>1.0 × ULN	>1.0 × baseline													2	0
	CSF RBC	Cells/mm^3	<1.0 × LLN	<1.0 × baseline	2	0			1	0	2	0	3	0	3	0	3	0
			>1.0 × ULN	>1.0 × baseline	2	0			1	0	2	0	3	1	3	0	3	0
	CSF neutrophils %	%	<1.0 × LLN	<1.0 × baseline			1	0					1	0				
			>1.0 × ULN	>1.0 × baseline			1	0					1	0				
	CSF lymphocytes %	%	<1.0 × LLN	<1.0 × baseline			1	0					1	0			1	0
			>1.0 × ULN	>1.0 × baseline			1	0					1	0			1	0

Includes data on and after 1st date of dose (Day 1).
Percentages are displayed for the laboratory tests having a category with ≥50 evaluable subjects.
Abs = absolute; APTT = activated partial thromboplastin time; CSF = cerebrospinal fluid; Hgb = haemoglobin; HPF = high power field; LLN = lower limit of normal; N = total number of subjects with abnormal baseline with at least one observation of the given laboratory test while on study treatment or during lag time; n = number of subjects with abnormal baseline with a laboratory abnormality meeting specified criteria while on study treatment or during lag time; PF = PF-04360365; Qual = qualitative; RBC = red blood cell; TSH = thyroid-stimulating hormone; ULN = upper limit of normal; WBC = white blood cell.

ECGs Results: A summary of categorical ECG findings is provided in Table 18. Abnormalities in ECG intervals were observed in subjects treated with ponezumab and placebo, with no clear differences between treatment groups. One (1) subject had calculating the heart rate-corrected QT interval by Fridericia's formula (QTcF) value >500 msec (ponezumab 8.5 mg/kg). No subject had a >60 msec increase from Baseline in QTcF.

Table 18. Summary of Categorical Electrocardiogram Findings

Parameter Criteria n (%)	Ponezumab 0.1 mg/kg (N=25)	Ponezumab 0.5 mg/kg (N=25)	Ponezumab 1.0 mg/kg (N=25)	Placebo Part A (N=24)	Ponezumab 3.0 mg/kg (N=32)	Ponezumab 8.5 mg/kg (N=31)	Placebo Part B (N=32)
QTcF (msec)							
450 to <480 msec	10 (40.0)	6 (24.0)	4 (16.0)	3 (12.5)	8 (25.0)	6 (19.4)	5 (15.6)
480 to <500 msec	0	1 (4.0)	1 (4.0)	0	0	1 (3.2)	1 (3.1)
≥500 msec	0	0	0	0	0	1 (3.2)	0
30 to <60 msec increase[a]	4 (16.0)	5 (20.0)	2 (8.0)	1 (4.2)	4 (12.5)	10 (32.3)	9 (28.1)
≥60 msec increase[a]	0	0	0	0	0	0	0
30 to <60 msec decrease[a]	0	0	0	0	0	0	0
≥60 msec decrease[a]	0	0	0	0	0	0	0
QTcB (msec)							
450 to <480 msec	7 (28.0)	7 (28.0)	6 (24.0)	7 (29.2)	9 (28.1)	6 (19.4)	7 (21.9)
480 to <500 msec	2 (8.0)	0	1 (4.0)	0	0	1 (3.2)	2 (6.3)
≥500 msec	0	0	0	0	0	1 (3.2)	0
30 to <60 msec increase[a]	4 (16.0)	7 (28.0)	2 (8.0)	6 (25.0)	12 (37.5)	10 (32.3)	13 (40.6)
≥60 msec increase[a]	1 (4.0)	0	1 (4.0)	0	0	2 (6.5)	0
30 to <60 msec decrease[a]	0	0	0	0	0	0	0
≥60 msec decrease[a]	0	0	0	0	0	0	0
PR interval (msec)							
≥300	0	0	0	1 (4.2)	1 (3.1)	0	0
≥25%/50% increase[a]	0	0	0	0	1 (3.1)	0	0
≥25%/50% decrease[a]	0	0	0	0	0	0	0
QRS complex (msec)							
≥200	0	0	0	0	0	0	0
≥25%/50% increase[a]	0	0	1 (4.0)	0	0	0	0
≥25%/50% increase[a]	0	0	0	0	0	0	0

N = total number of subjects in the treatment group in the indicated population; n = number of subjects whose post baseline value met the criterion; PR = in electrocardiography, the interval between the start of the P wave and the start of the QRS complex, corresponding to the time between the onset of atrial depolarization and onset of ventricular depolarization; QRS = the deflections in the tracing of the electrocardiogram, comprising the Q, R, and S waves, that represent the ventricular activity of the heart (the depolarization of the ventricles); QTcF = QTc corrected for heart rate using Fridericia's formula; QTcB = QTc corrected for heart rate using Bazett's formula.

a. From baseline, where baseline was defined as the latest non-missing value from a range of pretreatment values.

Brain MRI: A summary of brain MRI clinical findings at baseline and at any visit postbaseline is provided in Table 19. The most commonly observed brain MRI abnormality present at Baseline was mild white matter pigmentation (range, 72% to 88%). There were changes from Baseline in brain MRI abnormalities. The most commonly observed brain MRI abnormality present at any visit was other abnormality (range, 26% to 48%) and microhemorrhage (range, 8% to 28%; 34 subjects). Other MRI brain abnormalities that occurred postbaseline at any visit included cerebral edema (1 subject), cerebral/meningeal enhancement (1 subject), subdural hematoma (1 subject), cortical infarcts (4 subjects), subcortical grey matter infarcts (2 subjects), white matter infarcts (3 subjects), and white matter hyperintensities (13 subjects).

Table 19. Summary of Brain MRI Clinical Findings

Number (%) of Subjects	Ponezumab 0.1 mg/kg (N=25)	Ponezumab 0.5 mg/kg (N=25)	Ponezumab 1.0 mg/kg (N=25)	Placebo Part A (N=24)	Ponezumab 3.0 mg/kg (N=32)	Ponezumab 8.5 mg/kg (N=31)	Placebo Part B (N=32)
Baseline, N	25	25	25	24	32	31	32
Cerebral edema	0	0	0	0	0	0	0
Cerebral/Meningeal enhancement	0	0	0	1 (4.2)	0	0	0
Microhemorrhage	3 (12.0)	1 (4.0)	0	2 (8.3)	1 (3.1)	2 (6.5)	3 (9.4)
Parenchymal hematoma	4 (16.0)	2 (8.0)	5 (20.0)	5 (20.8)	4 (12.5)	10 (32.3)	7 (21.9)
Subarachnoid hemorrhage	0	0	0	0	0	0	0
Subdural hematoma	0	0	0	0	0	0	0
Cortical infarcts	0	0	0	0	0	0	0
Subcortical gray matter infarcts	2 (8.0)	0	2 (8.0)	2 (8.3)	2 (6.3)	2 (6.5)	1 (3.1)
White matter infarcts	0	0	0	0	1 (3.1)	1 (3.2)	0
White matter hyperintensities	1 (4.0)	0	0	2 (8.3)	1 (3.1)	2 (6.5)	1 (3.1)
Mild	18 (72.0)	20 (80.0)	18 (72.0)	17 (77.3)	28 (87.5)	25 (80.6)	25 (78.1)
Moderate	7 (28.0)	4 (16.0)	7 (28.0)	5 (22.7)	3 (9.4)	6 (19.4)	7 (21.9)
Severe	0	1 (4.0)	0	0	0	0	0
Other abnormality	7 (28.0)	5 (20.0)	5 (20.0)	9 (37.5)	10 (31.3)	10 (32.3)	9 (28.1)
Change from Baseline to any visit postbaseline, N	25	25	25	24	31	28	32
Cerebral edema	0	1 (4.0)	0	0	0	0	0
Cerebral/Meningeal enhancement	0	1 (4.0)	0	0	0	0	0
Gadolinium used	3 (12.0)	1 (4.0)	2 (8.0)	1 (4.2)	1 (3.2)	2 (7.1)	3 (9.4)
Microhemorrhage	4 (16.0)	7 (28.0)	2 (8.0)	6 (25.0)	3 (9.7)	6 (21.4)	6 (18.8)
Parenchymal hematoma	0	0	0	0	0	0	0
Subarachnoid hemorrhage	0	0	0	0	0	0	0
Subdural hematoma	0	1 (4.0)	0	0	0	0	0
Cortical infarcts	1 (4.0)	0	2 (8.0)	0	0	1 (3.6)	0
Subcortical gray matter infarcts	0	0	0	0	1 (3.2)	1 (3.6)	0
White matter infarcts	0	1 (4.0)	0	0	0	0	2 (6.3)
White matter hyperintensities	0	3 (12.0)	2 (8.0)	2 (8.3)	4 (12.9)	0	2 (6.3)
Other abnormality	12 (48.0)	9 (36.0)	9 (32.0)	10 (41.7)	8 (25.8)	12 (42.9)	10 (31.3)

Post baseline data presented is the change from previous visit assessment (except for Gadolinium used).
Unplanned visit used for analyses only in the Baseline and any visit post baseline time points.
MRI = magnetic resonance imaging; N = number of subjects.

ADAs: No ADAs (immunogenicity response) were detected in any of the serum samples from this study. Clinician review of the physical and neurological evaluations across all study sites did not reveal any patterns of change between screening and last subject visit that the Investigator deemed to be clinically significant.

CONCLUSIONS:

- Ponezumab was safe and well tolerated after multiple doses of up to 8.5 mg/kg over an 18-month treatment period with 6 months post treatment safety follow-up in 138 subjects exposed to ponezumab. There were 3 subjects with treatment-related SAEs (1 ponezumab 0.1 mg/kg, 1 ponezumab 0.5 mg/kg, and 1 Part A placebo subject) and 3 deaths (1 active [ponezumab 0.5 mg/kg] and 2 Part B placebo), which were not treatment-related. The most commonly reported SAEs were myocardial infarction, delirium, pneumonia, prostate cancer, subdural hygroma, hip fracture, humerus fracture, syncope, seizure, atrial fibrillation, pulmonary embolism, and benign prostatic hypertrophy.

- Ponezumab exhibited dose-dependent increases in plasma concentrations, limited plasma accumulation, low CSF penetration, and negligible appearance in the urine.

- Both plasma Aβ1-x and Aβ1-40 exhibited robust increases from Baseline at each dose level.The time course of CSF biomarkers did not appear to differ substantially for placebo- versus ponezumab-treated subjects, nor was there any discernable dose response. The appearance of Aβ1-x in the urine was negligible.

- Serum ADAs for ponezumab were not detected in any subjects in this study.

- The point estimates for the differences in LS means for ADAS-cog consistently favored placebo and the point estimates for the differences in LS means for DAD favored placebo for 3 of 5 ponezumab doses studied. However, all of the 90% CIs for the differences in LS means between ponezumab and placebo in the mean change from Baseline to Day 570 (MMRM inferential analysis) for ADAS-cog and DAD total scores overlapped 0 for Part A or Part B of the study. Further inference is therefore limited for these secondary efficacy endpoints due to the limited sample size.