PFIZER INC.

These results are supplied for informational purposes only.
Prescribing decisions should be made based on the approved package insert.

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

PROTOCOL NO.: A9951007 (PIB/PET IMAGING)

PROTOCOL TITLE: A Phase 2 Double-Blinded, Randomized, Placebo-Controlled, Multicenter Study Evaluating the Safety, Tolerability and Pharmacokinetics/Pharmacodynamics of PF-04360365 in Mild to Moderate Alzheimer's Disease Patients

Study Centers: Three (3) centers in Sweden took part in the study and randomized subjects.

Study Initiation and Final Completion Dates: 06 August 2009 to 01 June 2011

Phase of Development: Phase 2

Study Objectives:

Primary Objectives:

- To evaluate safety, tolerability and pharmacokinetics (PK) of multiple doses of PF-04360365 administered monthly (approximately every 30 days; Cohort M) or every 3 months (approximately every 90 days; Cohort Q) for approximately 1 year in subjects with mild-to-moderate Alzheimer's Disease (AD).

- To assess the effect of multiple doses of PF-04360365 on brain amyloid burden in the subjects dosed monthly (Cohort M) for approximately 1 year in subjects with mild-to-moderate AD.

- To characterize the effect of PF-04360365 on cerebrospinal fluid (CSF) amyloid beta (Aβ) species during dosing for approximately 1 year.

Secondary Objectives:

- To examine the efficacy of PF-04360365, as assessed by the 70-point Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-cog), the Disability Assessment for Dementia (DAD) scales, and the Mini Mental State Examination (MMSE) in subjects with mild-to-moderate AD during and following dosing for approximately 1 year.

- To examine the effect of PF-04350365 on plasma Aβ species during and following dosing for approximately 1 year.

METHODS

Study Design: This was a Phase 2 double-blind, placebo-controlled, randomized study evaluating the safety, tolerability, PK and pharmacodynamics (PD) following multiple doses of PF-04360365 in approximately 36 mild-to-moderate AD subjects. Subjects were enrolled in either monthly (Cohort M) or quarterly (Cohort Q) dosing cohorts. Cohort Q was enrolled first. Within each cohort, subjects were randomized in a 2:1 ratio, active:placebo. Cohort Q received 10 mg/kg PF-04360365 or placebo every 3 months (n=18 per cohort; n=12 PF-04360365, n=6 placebo). Cohort M received an initial single loading dose of 10 mg/kg PF-04360365 or placebo followed by monthly doses of 7.5 mg/kg PF-04360365 or placebo (n=18 per cohort; n=12 PF-04360365, n=6 placebo).

The screening visit took place within 60 days of the Baseline visit (Day 0). Post-baseline visits took place on Day 1, Day 30 (Month 1), Day 40, Day 50, Day 60 (Month 2), then at Months 3, 6, 7, 9, 12, 13 and 18/Follow-Up visit. The Schedule of Activities (Cohort Q and Cohort M) are presented in Table 1 and Table 2. The study schematic is presented in Figure 1.

Table 1. Schedule of Activities – Cohort Q

Study Activity	**Screening**	**Baseline**	**M 0**	**M 1**			**M 2**	**M 3**	**M 6**	**M 7**	**M 9**	**M 12**	**M 13**	**M 18/ Follow-Up**
Visit Window (Days)				**±2**	**±2**	**±2**	**±2**	**±3**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**
Approximate Study Day	**D 60 to -1**	**D 7 to 0**	**D 1**	**D 30**	**D 40 Group 1**	**D 50 Group 2**	**D 60 Group 3**	**D 90**	**D 180**	**D 210**	**D 270**	**D 360**	**D 390**	**D 540**
Informed consent/assent	X													
Review inclusion/exclusion criteria	X	X												
Complete medical & surgical history	X													
Drug, alcohol & tobacco use	X													
Full physical/neurological exams	X												X	X
Brief physical/neurological exams			X					X	X		X	X		
Rosen-Modified Hachinski Ischemia	X													
Concomitant medications	X	X	X	X	X	X	X	X	X		X	X	X	X
Height and weight[a]	X[a]	X	X					X	X		X	X	X	X
Supine vital signs	X	X	X					X	X		X	X	X	X
Safety laboratory tests	X	X						X	X		X	X		X
AE monitoring		X	X	X	X	X	X	X	X		X	X	X	X
PK/PD blood sampling[b]			X		X	X	X	X	X		X	X	X	X
LP: PK/PD CSF sampling[c]		X			Group 1[c]	Group 2	Group 3[c]	Group 1	Groups 2 and 3			X		
PK/PD urine sampling			X					X	X			X		
Immunogenicity[d]			X					X	X		X	X		X
Study drug administration			X					X	X		X	X		
ApoE genotyping		X												
ADAS-cog[e]		X						X	X		X		X	X
MMSE[e]	X	X											X	
DAD[e]		X							X				X	X
ECG	X		X					X	X		X	X		X
MRI	X[f]									X			X	
Telephone visit				X										

Table 1. Schedule of Activities – Cohort Q

ADAS-cog = Alzheimer's disease assessment scale cognitive subscale; AE = adverse event; ApoE = Apolipoprotein E; CSF = cerebrospinal fluid; D = day; DAD = disability assessment for dementia; ECG = electrocardiogram; LP = lumbar puncture; M = month; MMSE = mini mental state examination; MRI = magnetic resonance imaging; PD = pharmacodynamics; PI = Principal Investigator; PK = pharmacokinetic.

a. Height was measured only at Screening.

b. PK/PD blood was sampled prior to infusion and 5 minutes following completion of the infusion at Months 0, 3, 6, 9 and 12. Additional PK/PD blood samples were also taken on Day 40 (Group 1), Day 50 (Group 2), and Day 60 (Group 3). In addition, PK/PD blood samples were taken at Months 13 and 18 (Follow-up) for Cohort Q.

c. All LP sampling that coincided with dosing were obtained prior to infusion. Subjects in Cohort Q were randomly assigned to have CSF samples taken. PK/PD sampling with Group 1 on Day 40; Group 2 on Day 50; or Group 3 on Day 60 (Month 2) pre-infusion. Subjects assigned to receive the Day 40 sample (Group 1) received their third LP at Month 3 prior to infusion; these subjects did not have CSF sampling at Month 6. All other subjects in Cohort Q (Groups 2 and 3) had CSF sampling at Month 6 prior to infusion. All subjects in Cohort Q had CSF PK/PD sampling at Baseline and Month 12 pre-infusion. It was recommended that LPs were performed prior to the day of dosing; however, per PI's discretion, LPs could have been performed pre dose on the day of dosing.

d. Immunogenicity sample obtained on each day of study drug administration prior to infusion and at Month 18 (Follow-up).

e. Performed prior to infusion; could have been performed on the day of dosing, per PI's discretion, as long as subject was not fasting.

f. Screening brain MRI read should have been received prior to first LP and first dose. If the MRI could not be obtained within a short period of time preceding the LP, a careful fundoscopic exam must have been conducted and documented to specifically rule out papilledema or any other eye findings that would have suggested raised intracranial pressure.

Table 2. Schedule of Activities – Cohort M

Study Activity	**Screen**	**Base line**	**M 0**			**M 1**	**M 2**	**M 3**	**M 4**	**M 5**	**M 6**	**M 7**	**M 8**	**M 9**	**M 10**	**M 11**	**M 12**	**M 13**	**M 18 / Follow-Up**
Visit Window (Days)				**±1**	**±2**	**±2**	**±2**	**±3**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**
Approximate Study Day	**D 60 to -1**	**D 7 to 0**	**D 1**	**D 10 Group 4**	**D 20 Group 5**	**D 30**	**D 60**	**D 90**	**D 120**	**D 150**	**D 180**	**D 210**	**D 240**	**D 270**	**D 300**	**D 330**	**D 360**	**D 390**	**D 540**
Informed consent/assent	X																		
Review inclusion / exclusion criteria	X	X																	
Complete medical & surgical history	X																		
Full physical / neurological exams	X																	X	X
Brief physical / neurological exams			X			X		X			X			X			X		
Drug, alcohol and tobacco use	X																		
Rosen-Modified Hachinski Ischemia	X																		
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Height and weight[a]	X[a]	X	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X
Supine vital signs	X	X	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X
Safety laboratory tests	X	X						X			X			X			X		X
Adverse event monitoring		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PK/PD blood sampling[b]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
LP: PK/PD CSF sampling[c]		X		Group 4	Group 5	Group 6					X[c]						X		
PK/PD urine sampling			X					X			X						X		
Immunogenicity[d]			X			X	X	X	X	X	X	X	X	X	X	X	X		

Table 2. Schedule of Activities – Cohort M

Study Activity	Screen	Base line	M 0			M 1	M 2	M 3	M 4	M 5	M 6	M 7	M 8	M 9	M 10	M 11	M 12	M 13	M 18 / Follow-Up
Visit Window (Days)				±1	±2	±2	±2	±3	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7
Approximate Study Day	D 60 to -1	D 7 to 0	D 1	D 10 Group 4	D 20 Group 5	D 30	D 60	D 90	D 120	D 150	D 180	D 210	D 240	D 270	D 300	D 330	D 360	D 390	D 540
Study drug administration			X			X	X	X	X	X	X	X	X	X	X	X	X		
ApoE genotyping		X																	
ADAS-cog[e]		X						X			X			X					
MMSE[e]	X	X																X	
DAD[e]		X									X							X	X
ECG	X		X					X			X			X			X		X
MRI	X[f]							X				X						X	
Amyloid imaging	X																	X	

ADAS-cog = Alzheimer's disease assessment scale cognitive subscale; ApoE = Apolipoprotein E; CSF = cerebrospinal fluid; D = day; DAD = disability assessment for dementia; ECG = electrocardiogram; LP = lumbar puncture; M = month; MMSE = mini mental state examination; MRI = magnetic resonance imaging; PD = pharmacodynamics; PI = Principal Investigator; PK = pharmacokinetic.

a. Height was measured only at Screening.

b. PK/PD blood was sampled prior to infusion and 5 minutes following completion of the infusion at Months 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, and 12. Additional PK/PD blood samples were taken on Day 10 (Group 4) and Day 20 (Group 5). In addition, PK/PD blood samples were taken at Months 13 and 18 (Follow-up) for Cohort M.

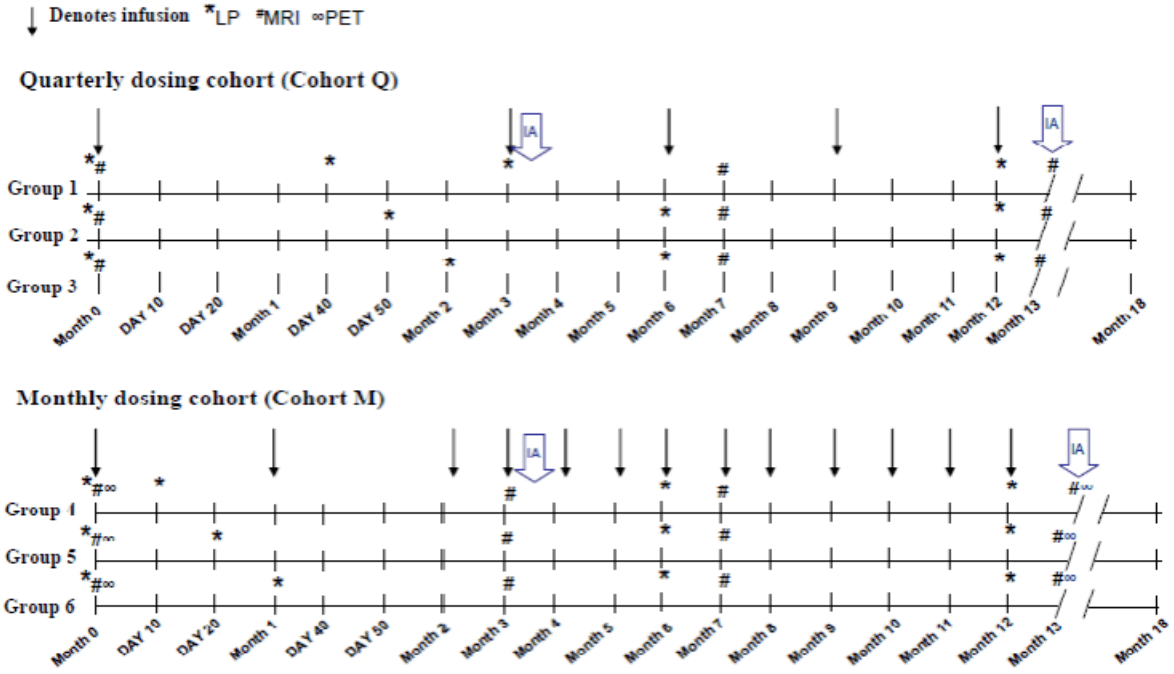
c. All LP sampling that coincided with dosing was obtained prior to infusion. Subjects in Cohort M were randomly assigned to have CSF PK/PD sampling with: Group 4 on Day 10; Group 5 on Day 20 and Group 6 on Day 30 (Month 1) pre-infusion. All subjects were to also have CSF PK/PD sampling at Baseline and Months 6 and 12 pre-infusion. It was recommended that LPs be performed prior to the day of dosing; however, per PI's discretion, LPs could have been performed pre dose on the day of dosing.

d. Immunogenicity sample obtained on each day of study drug administration prior to infusion and at Month 18 (Follow-up).

e. Performed prior to infusion; was performed on the day of dosing, per PI's discretion, as long as subject was not fasting.

f. Screening brain MRI read should have been received prior to first LP and first dose. If the MRI could not be obtained within a short period of time preceding the LP, a careful fundoscopic exam must have been conducted and documented to specifically rule out papilledema or any other eye findings that would have suggested raised intracranial pressure.

Figure 1 Study Schematic



IA = interim analysis; LP = lumbar puncture; MRI = magnetic resonance imaging; PET = positron emission tomography.

Number of Subjects (Planned and Analyzed): Thirty six (36) subjects were planned and assigned to the study treatment.

Diagnosis and Main Criteria for Inclusion and Exclusion: Male and female subjects of non childbearing potential, ≥50 years of age, with a diagnosis of probable AD, consistent with criteria from both the National Institute of Neurological and Communicative Disorders and Stroke and Alzheimer's Disease and Related Disorders Association and Diagnostic and Statistical Manual of Mental Disorders were eligible for inclusion. Subjects were to have a MMSE score of 16 to 26 at Screening and a Rosen-Modified Hachinski Ischemia score of ≤4.

Main Exclusion Criteria: Subjects with a diagnosis or history of other demential or neurodegenerative disorders; diagnosis or history of clinically significant cerebrovascular disease; specific exclusionary findings on brain magnetic resonance imaging (MRI); cortical infarct, >2 microhemorrhages, or multiple white matter lacunes; history of autoimmune disorders; or history of allergic or anaphylactic reactions were excluded from the study.

Study Treatment: PF-04360365 and matching placebo were supplied as a frozen liquid formulation for IV administration. Cohort Q received 10 mg/kg PF-04360365 or placebo every 3 months (n=18 per cohort; n=12 PF-04360365, n=6 placebo). Cohort M received an initial single loading dose of 10 mg/kg PF-04360365 or placebo followed by monthly doses of 7.5 mg/kg PF-04360365 or placebo (n=18 per cohort; n=12 PF-04360365, n=6 placebo). PF-04360365 or placebo was administered by intravenous infusion over approximately 10 minutes. The treatment duration was approximately 1 year.

Efficacy and Safety Endpoints:

Primary Endpoints:

1. Safety endpoints included adverse events (AEs), physical/neurological exams, vital signs, 12-lead electrocardiogram (ECG), clinical laboratory values (including CSF labs), brain MRI, immunogenicity and cognitive assessments.

2. Change from Baseline in amyloid load as assessed by positron emission tomography (PET) imaging at Month 13 in a subset of subjects (Cohort M).

3. Plasma and CSF concentrations (as available) of PF-04360365.

4. CSF concentrations of Aβ species.

Secondary Endpoints:

1. Change from Baseline on the ADAS-cog total scores at Months 3, 6, 9, 13 and 18.

2. Change from Baseline on the DAD total scores at Months 6, 13 and 18.

3. Change from Baseline on the MMSE total scores at Month 13.

4. Plasma concentration of Aβ species.

Safety Evaluations: Safety evaluations included AEs, physical and neurological examinations, vital signs, 12-lead ECG, clinical laboratory values (including CSF proteins), brain MRI, and immunogenicity.

Statistical Methods:

Analysis Sets:

Full Analysis Set (FAS): The FAS comprised all randomized subjects who received at least 1 infusion of study medication.

Per Protocol (PP) Analysis Set: The PP analysis set comprised all subjects within the FAS who received the study drug infusions consistent with the study requirements, had successful PET scans at the Month 13 (Day 390) visit, and had no major protocol deviations.

Safety Analysis Set: The safety analysis set comprised all randomized subjects who received at least 1 infusion of study medication.

Primary Statistical Endpoints and Analysis: Amyloid burden was determined from the linear model and results presented with confidence interval (CI). No hypotheses were generated for this comparison. No statistical hypotheses were generated for estimation of plasma and CSF concentrations of PF-04360365 and its effect on CSF Aβ.

Analysis of covariance (ANCOVA) was used to compare the mean change from Baseline for amyloid load at the Month 13 visit (approximately 30 days following the last study drug infusion) as measured by the PET imaging endpoint standard uptake volume ratio (SUVR).

Secondary Statistical Endpoints and Analysis: No statistical hypothesis was generated for plasma Aβ concentration-time data. The effects of PF-04360365 on cognitive and functional assessment were not known and the visit-wise comparison was to be used in the future for further refinement of the hypothesis generation. The analysis for ADAS-cog and DAD total scores was a mixed model repeated measures analysis and carried out on the FAS with the response as the change from baseline of the total score. The analysis for MMSE total scores used ANCOVA.

RESULTS

Subject Disposition and Demography: A total of 36 subjects were screened and assigned study treatment. All subjects, except 1 subject in Cohort M who received placebo, completed the study. This subject was discontinued from the study due to no longer being willing to participate. Two (2) subjects were discontinued from study treatment, but remained in the study. Summaries of subject disposition and evaluation groups are presented in Table 3 and Table 4, respectively.

Table 3. Summary of Subject Disposition and Evaluation Groups

Number of Subjects	Cohort Q		Cohort M	
	PF-04360365 10 mg/kg	Placebo	PF-04360365 10 mg or 7.5 mg/kg	Placebo
Screened: 36				
Assigned to study treatment: 36				
Treated	12	6	12	6
Completed	12	6	12	5
Discontinued from the study	0	0	0	1
Drug-related AEs	0	0	0	0[a]
Non drug-related AEs	0	0	0[b]	0
No longer willing to participate in study	0	0	0	1[a]

AEs = adverse events; FAS = full analysis set; PK = pharmacokinetic; PP = per protocol.

a. One (1) subject discontinued study treatment due to a drug-related AE, but remained in the study. This subject subsequently discontinued from the study during the post-therapy Follow-Up period.

b. One (1) subject discontinued study treatment due to a non-drug related AE, but remained in the study and is thus marked as having completed the study.

Table 4. Subject Evaluation Groups

Number of Subjects	Cohort Q		Cohort M	
	PF-04360365 10 mg/kg	Placebo	PF-04360365 10 mg or 7.5 mg/kg	Placebo
Subjects analyzed for efficacy:				
FAS	12	6	12	6
PP analysis set	0	0	12	6
PK analysis set	12	0	12	0
Safety analysis set	12	6	12	6

FAS = full analysis set; PK = pharmacokinetic; PP = per protocol.

Subjects included 21 males and 15 females who had mild-to-moderate AD. All 36 subjects were White. Subjects ranged in age from 53 to 84 years of age, ranged in weight from 55.0 to 91.0 kg, and had a total mean body mass index ranging from 20.8 to 28.9 kg/m^2. Demographic characteristics were broadly similar among all treatment groups. The summary of demographic characteristics is presented in Table 5.

Table 5. Summary of Demographic Characteristics

Characteristics	Cohort Q						Cohort M					
	PF-04360365 10 mg/kg			Placebo			PF-04360365 10 mg/kg/7.5 mg/kg			Placebo		
	M	F	Total	M	F	Total	M	F	Total	M	F	Total
Number of subjects	8	4	12	3	3	6	9	3	12	1	5	6
Age (years):												
<50	0	0	0	0	0	0	0	0	0	0	0	0
50-59	3	1	4	0	0	0	1	0	1	0	2	2
60-69	4	0	4	1	2	3	5	1	6	0	1	1
70-79	1	3	4	2	0	2	2	1	3	1	2	3
80-85	0	0	0	0	1	1	1	1	2	0	0	0
>85	0	0	0	0	0	0	0	0	0	0	0	0
Mean	62.0	71.3	65.1	72.0	70.7	71.3	68.4	73.7	69.8	72.0	64.6	65.8
SD	4.8	8.3	7.4	5.3	12.2	8.5	7.5	7.4	7.5		8.6	8.3
Range	55-70	59-77	55-77	68-78	60-84	60-84	59-81	68-82	59-82	72-72	53-72	53-72
Race												
White	8	4	12	3	3	6	9	3	12	1	5	6
Weight (kg)												
Mean	73.4	67.3	71.4	80.8	67.8	74.3	73.6	60.5	70.3	91.0	69.0	72.7
SD	7.8	3.8	7.2	8.0	4.3	9.1	7.0	4.8	8.7		6.9	10.9
Range	63.0-87.5	63.3-71.0	63.0-87.5	73.8-89.5	64.0-72.5	64.0-89.5	64.6-84.0	55.0-64.2	55.0-84.0	91.0-91.0	60.1-79.1	60.1-91.0
BMI (kg/m^2)												
Mean	23.5	25.3	24.1	25.5	26.4	26.0	23.2	22.4	23.0	26.6	24.8	25.1
SD	2.5	2.4	2.5	3.0	1.5	2.2	2.0	0.8	1.8		2.7	2.5
Range	20.9-28.6	22.7-27.4	20.9-28.6	23.3-28.9	24.7-27.6	23.3-28.9	20.8-26.2	21.8-23.3	20.8-26.2	26.6-26.6	21.3-27.6	21.3-27.6
Height (cm)												
Mean	177.0	163.3	172.4	178.0	160.3	169.2	178.3	164.3	174.8	185.0	166.8	169.8
SD	8.0	3.3	9.4	2.0	2.1	9.8	7.8	5.7	9.5		4.0	8.2
Range	165-186	160-167	160-186	176-180	158-162	158-180	166-191	158-169	158-191	185-185	160-170	160-185

BMI was calculated as $weight/(height*0.01)^2$.
BMI = body mass index; F = female; M = male; SD = standard deviation.

Efficacy, Pharmacokinetic and Pharmacodynamic Results:

Primary Efficacy Results: For the overall brain, the least squares (LS) mean (90% CI) for percent change from Baseline in SUVR for placebo was -1.07 (-6.76, 4.97) and for PF-04360365 was -2.48 (-6.47, 1.68). The difference in LS means (PF-04360365 minus placebo) was -1.43 with a 90% CI of (-8.35, 6.02) which overlaps 0. Mean change in SUVR at Month 13 (PP Analysis Set) is presented in Table 6.

Table 6. Mean Change in SUVR at Month 13 (PP Analysis Set)

Treatment					Difference From Placebo			
	N[a]	LS Mean	SE	90% CI	LS Mean	SE	90% CI	p-Value
PF-04360365	12	-2.48	0.024	(-6.47, 1.68)	-1.43	0.042	(-8.35, 6.02)	0.734
Placebo	6	-1.07	0.034	(-6.76, 4.97)				

Based on an ANOVA model with terms for treatment as fixed effects and Baseline value as the covariate.
Combined across brain region was defined as the geometric mean for change in SUVR across all brain regions.
Cerebellum was excluded from calculation of combined across brain region because SUVR was calculated relative to the cerebellum.
Percent change from Baseline values were calculated by back-transforming the change from Baseline values on the log scale, subtracting 1, and multiplying by 100.
ANOVA = analysis of variance; CI = confidence interval; LS = least squares; N = number of subjects; PP = per protocol; SE = standard error; SUVR = standard uptake volume ratio.
a. Represents the number of subjects included in the analysis.

The largest treatment difference was seen in the occipital cortex, where the LS mean (90% CI) for percent change from Baseline in SUVR for placebo was 1.58 (-4.40, 7.93) and for PF-04360365 was -2.17 (-6.27, 2.11). The difference in LS means (PF-04360365 minus placebo) was -3.69 with a 90% CI of (-10.59, 3.75) which overlaps 0.

Secondary Efficacy Results: For Cohort Q at Month 13, the difference in LS means (PF-04360365 minus placebo) for change from Baseline in ADAS-cog total score was -1.36, with a 90% CI of (-8.38, 5.66) which overlaps 0. For Cohort M at Month 13, the difference in LS means (PF-04360365 minus placebo) for change from Baseline in ADAS-cog total score was 4.74, with a 90% CI of (-2.77, 12.25) which overlaps 0. The analysis of change from Baseline in ADAS-cog total score (FAS) is summarized in Table 7.

Table 7. Analysis of Change From Baseline in ADAS-cog Total Score - FAS

	N1	N2	LS Mean Treatment Group Difference (SE)	90% Confidence Limits	p-Values
Cohort Q[a] PF-04360365 vs placebo in Month 13	11	5	-1.36 (4.223)	(-8.38, 5.66)	0.7486
Cohort M[b] PF-04360365 vs placebo in Month 13	12	3	4.74 (4.522)	(-2.77, 12.25)	0.2968

ADAS-cog = Alzheimer's disease assessment scale cognitive subscale; FAS = full analysis set; N1 = number of subjects in the PF-04360365 group; N2 = number of subjects in the placebo group; LS = least squares; SE = standard error; vs = versus.
a. Dose of PF-04360365 was 10 mg/kg.
b. Dose of PF-04360365 was either 10 mg/kg or 7.5 mg/kg.

For Cohort Q at Month 13, the difference in LS means (PF-04360365 minus placebo) for change from Baseline in DAD total score was 11.37, with a 90% CI of (-3.31, 26.06) which overlaps 0. For Cohort M at Month 13, the difference in LS means (PF-04360365 minus placebo) for change from Baseline in DAD total score was -0.10, with a 90% CI of (-15.72, 15.52) which overlaps 0. The analysis of change from Baseline in DAD total score (FAS) is presented in Table 8.

Table 8. Analysis of Change From Baseline in DAD Total Score - FAS

	N1	N2	LS Mean Treatment Group Difference (SE)	90% Confidence Limits	p-Values
Cohort Q[a] PF-04360365 vs placebo in Month 13	12	6	11.37 (8.789)	(-3.31, 26.06)	0.2007
Cohort M[b] PF-04360365 vs placebo in Month 13	12	5	-0.10 (9.354)	(-15.72, 15.52)	0.9918

DAD = disability assessment for dementia; FAS = full analysis set; N1 = number of subjects in the PF-04360365 group; N2 = number of subjects in the placebo group; LS = least squares; SE = standard error; vs = versus.
a. Dose of PF-04360365 was 10 mg/kg.
b. Dose of PF-04360365 was either 10 mg/kg or 7.5 mg/kg.

For Cohort Q at Month 13, the difference in LS means (PF-04360365 minus placebo) for change from Baseline in MMSE total score was 1.35 with a 90% CI (-1.90, 4.60), which overlaps 0. For Cohort M at Month 13, the difference in LS means (PF-04360365 minus placebo) for change from Baseline in MMSE total score was 1.45 with a 90% CI (-2.27, 5.16), which overlaps 0. The analysis of change from Baseline in MMSE total score (FAS) is presented in Table 9.

Table 9. Analysis of Change From Baseline at Month 13 for MMSE Total Score-FAS

	N1	N2	LS Mean Treatment Group Difference (SE)	90% Confidence Limits	p-Values
Cohort Q[a] PF-04360365 vs placebo in Month 13	12	6	1.35 (1.910)	(-1.90, 4.60)	0.4855
Cohort M[b] PF-04360365 vs placebo in Month 13	12	4	1.45 (2.185)	(-2.27, 5.16)	0.5132

FAS = full analysis set; MMSE = mini mental state examination; N1 = number of subjects in the PF-04360365 group; N2 = number of subjects in the placebo group; LS = least squares; SE = standard error; vs = versus.
a. Dose of PF-04360365 was 10 mg/kg.
b. Dose of PF-04360365 was either 10 mg/kg or 7.5 mg/kg.

Pharmacokinetic Results: Plasma concentration-time profiles for PF-04360365 for both Cohorts M and Q exhibited dose-dependent increases in plasma concentrations. There was limited mean accumulation following multiple dosing: 1.0- and 1.5-fold for Cohort M based on plasma concentration at the end of the infusion (C_{end}) and trough plasma concentration (C_{trough}) calculations, respectively; and 1.2- and 1.3-fold for Cohort Q based on C_{end} and C_{trough} calculations, respectively. PF-04360365 was quantifiable in the CSF of every subject who received active treatment. Mean CSF/plasma ratios for PF-04360365 were <1.0%. PF-04360365 was not quantifiable in the urine of any subject in this study.

Pharmacodynamic Results: CSF Aβ biomarkers, tau, and p-tau were quantifiable in the majority of subjects, however, in general, concentrations were highly variable and there appeared to be substantial overlap between subjects who received active treatment versus placebo treatment. No $A\beta_{1-x}$ was detected in the urine of any subject. Robust increases from Baseline were observed in plasma for both $A\beta_{1-40}$ and $A\beta_{1-x}$. The mean increases from Baseline for plasma $A\beta_{1-40}$ at Month 12 were approximately 788-fold and 320-fold for Cohorts M and Q, respectively. In general, a similar pattern was observed for mean plasma $A\beta_{1-x}$ concentration-time profiles, with approximately 587-fold and 492-fold increases from baseline for Cohorts M and Q, respectively, at Month 12. Plasma $A\beta_{1-42}$ was quantifiable in <40% of the subjects in this study, and revealed only negligible changes from Baseline in the 1 PF-04360365-treated subject who exhibited a complete plasma concentration-time profile across the duration of the study.

Safety Results:

Serious Adverse Events (SAEs): Treatment-emergent SAEs (all causalities) are presented in Table 10. None of the SAEs were considered to be related to the study treatment.

Table 10. Treatment-Emergent Serious Adverse Events (All Causalities)

Number of Subjects With Adverse Events by: System Organ Class and MedDRA (v14.1) Preferred Term	Cohort Q PF-04360365 10 mg/kg	Cohort M PF-04360365 10 mg/kg /7.5 mg/kg	Cohort Q Placebo	Cohort M Placebo
	n (%)	n (%)	n (%)	n (%)
Evaluable for adverse events	12	12	6	6
With adverse events	2 (16.7)	1 (8.3)	1 (16.7)	0
Cardiac disorders	0	1 (8.3)	0	0
Myocardial infarction	0	1 (8.3)	0	0
Infections and infestations	1 (8.3)	0	0	0
Urinary tract infection	1 (8.3)	0	0	0
Injury, poisoning and procedural complications	1 (8.3)	0	0	0
Hip fracture	1 (8.3)	0	0	0
Nervous system disorders	0	0	1 (16.7)	0
Dementia Alzheimer's type	0	0	1 (16.7)	0

Subjects are only counted once per treatment for each row.
Includes all data collected since the first dose of study drug.
MedDRA (v14.1) coding dictionary applied.
MedDRA = Medical Dictionary for Regulatory Activities; v = version.

A total of 29 subjects had an AE, including 13 subjects who had an AE that was considered treatment-related. Treatment-emergent non serious AEs (all causalities) are presented in Table 11.

Adverse Events: The most frequently reported all-causality AEs (occurring in ≥2 subjects in any treatment group) were nasopharyngitis (6 subjects), fall (6 subjects), hypertension (5 subjects), depression (3 subjects), urinary tract infection (3 subjects), insomnia (3 subjects), cerebral microhemorrhage (3 subjects), arthralgia (3 subjects), headache (3 subjects), blood pressure increased (2 subjects), diarrhea (2 subjects), irritability (2 subjects), back pain (2 subjects), and myalgia (2 subjects).

The most commonly occurring treatment-related AEs (occurring in ≥2 subjects in any treatment group) were hypertension (5 subjects), cerebral microhemorrhage (3 subjects), blood pressure increased (2 subjects), irritability (2 subjects), and depression (2 subjects). The incidence of treatment-emergent AEs (treatment-related) is presented in Table 12.

Table 11. Treatment-Emergent Non Serious Adverse Events (All Causalities)

Number of Subjects With Adverse Events by: System Organ Class and MedDRA (v14.1) Preferred Term	Cohort Q PF-04360365 10 mg/kg n (%)	Cohort M PF-04360365 10 mg/kg /7.5 mg/kg n (%)	Cohort Q Placebo n (%)	Cohort M Placebo n (%)
Evaluable for adverse events	12	12	6	6
With adverse events	9 (75.0)	10 (83.3)	5 (83.3)	5 (83.3)
Cardiac disorders	0	1 (8.3)	0	0
Bradycardia	0	1 (8.3)	0	0
Eye disorders	0	0	0	2 (33.3)
Diplopia	0	0	0	1 (16.7)
Vision blurred	0	0	0	1 (16.7)
Gastrointestinal disorders	0	1 (8.3)	0	2 (33.3)
Diarrhoea	0	1 (8.3)	0	1 (16.7)
Vomiting	0	0	0	1 (16.7)
General disorders and administration site conditions	1 (8.3)	2 (16.7)	2 (33.3)	2 (33.3)
Facial pain	0	0	1 (16.7)	0
Irritability	0	1 (8.3)	0	1 (16.7)
Oedema	0	1 (8.3)	0	0
Oedema peripheral	0	0	1 (16.7)	0
Pyrexia	0	0	0	1 (16.7)
Tenderness	1 (8.3)	0	0	0
Infections and infestations	3 (25.0)	2 (16.7)	1 (16.7)	4 (66.7)
Bronchitis	0	0	0	1 (16.7)
Gastroenteritis	0	0	0	1 (16.7)
Influenza	0	0	0	1 (16.7)
Nasopharyngitis	1 (8.3)	2 (16.7)	0	3 (50.0)
Pneumonia	0	0	1 (16.7)	0
Urinary tract infection	2 (16.7)	0	0	0
Injury, poisoning and procedural complications	3 (25.0)	0	3 (50.0)	1 (16.7)
Fall	2 (16.7)	0	3 (50.0)	1 (16.7)
Post lumbar puncture syndrome	1 (8.3)	0	0	0
Upper limb fracture	0	0	1 (16.7)	0
Investigations	1 (8.3)	3 (25.0)	2 (33.3)	0
Alanine aminotransferase increased	1 (8.3)	0	0	0
Aspartate aminotransferase increased	1 (8.3)	0	0	0
Blood alkaline phosphatase increased	1 (8.3)	0	0	0
Blood pressure decreased	0	1 (8.3)	0	0
Blood pressure increased	0	2 (16.7)	0	0
Electrocardiogram QT prolonged	0	0	1 (16.7)	0

Table 11. Treatment-Emergent Non Serious Adverse Events (All Causalities)

Number of Subjects With Adverse Events by: System Organ Class and MedDRA (v14.1) Preferred Term	Cohort Q PF-04360365 10 mg/kg n (%)	Cohort M PF-04360365 10 mg/kg /7.5 mg/kg n (%)	Cohort Q Placebo n (%)	Cohort M Placebo n (%)
Evaluable for adverse events	12	12	6	6
With adverse events	9 (75.0)	10 (83.3)	5 (83.3)	5 (83.3)
Haemoglobin decreased	0	0	1 (16.7)	0
Weight decreased	0	1 (8.3)	0	0
Musculoskeletal and connective tissue disorders	4 (33.3)	3 (25.0)	0	1 (16.7)
Arthralgia	2 (16.7)	0	0	1 (16.7)
Back pain	1 (8.3)	1 (8.3)	0	0
Muscle rigidity	0	1 (8.3)	0	0
Musculoskeletal chest pain	1 (8.3)	0	0	0
Musculoskeletal stiffness	0	1 (8.3)	0	0
Myalgia	1 (8.3)	1 (8.3)	0	0
Nervous system disorders	3 (25.0)	4 (33.3)	1 (16.7)	1 (16.7)
Areflexia	0	1 (8.3)	0	0
Cerebral microhaemorrhage	1 (8.3)	1 (8.3)	0	1 (16.7)
Dizziness	0	1 (8.3)	0	0
Headache	2 (16.7)	1 (8.3)	0	0
Syncope	0	0	1 (16.7)	0
Psychiatric disorders	1 (8.3)	4 (33.3)	2 (33.3)	1 (16.7)
Anxiety	1 (8.3)	0	0	1 (16.7)
Depression	0	2 (16.7)	0	1 (16.7)
Disorientation	0	0	1 (16.7)	0
Insomnia	1 (8.3)	1 (8.3)	1 (16.7)	0
Sleep disorder	0	1 (8.3)	0	0
Renal and urinary disorders	0	1 (8.3)	0	0
Proteinuria	0	1 (8.3)	0	0
Respiratory, thoracic and mediastinal disorders	2 (16.7)	0	0	0
Cough	1 (8.3)	0	0	0
Oropharyngeal discomfort	1 (8.3)	0	0	0
Skin and subcutaneous tissue disorders	0	1 (8.3)	0	0
Rash	0	1 (8.3)	0	0
Vascular disorders	1 (8.3)	5 (41.7)	0	1 (16.7)
Haematoma	1 (8.3)	0	0	0
Hypertension	0	4 (33.3)	0	1 (16.7)
Orthostatic hypotension	0	1 (8.3)	0	0

Table 11. Treatment-Emergent Non Serious Adverse Events (All Causalities)

Number of Subjects With Adverse Events by: System Organ Class and MedDRA (v14.1) Preferred Term	Cohort Q PF-04360365 10 mg/kg	Cohort M PF-04360365 10 mg/kg /7.5 mg/kg	Cohort Q Placebo	Cohort M Placebo
	n (%)	n (%)	n (%)	n (%)
Evaluable for adverse events	12	12	6	6
With adverse events	9 (75.0)	10 (83.3)	5 (83.3)	5 (83.3)

Subjects are only counted once per treatment for each row.
Includes all data collected since the first dose of study drug.
MedDRA (v14.1) coding dictionary applied.
MedDRA = Medical Dictionary for Regulatory Activities; v = version.

Table 12. Incidence of Treatment-Emergent Adverse Events (Treatment-Related)

Number of Subjects With Adverse Events by: System Organ Class and MedDRA (v14.1) Preferred Term	Cohort Q: PF-04360365 10 mg/kg (N=12)	Cohort M: PF-04360365 10 mg/kg/7.5 mg/kg (N=12)	Cohort Q: Placebo (N=6)	Cohort M: Placebo (N=6)
	n	n	n	n
Cardiac disorders	0	1	0	0
Bradycardia	0	1	0	0
Eye disorders	0	0	0	2
Diplopia	0	0	0	1
Vision blurred	0	0	0	1
General disorders and administration site conditions	0	1	0	1
Irritability	0	1	0	1
Infections and infestations	0	1	0	1
Gastroenteritis	0	0	0	1
Nasopharyngitis	0	1	0	0
Injury, poisoning and procedural complications	0	0	1	0
Fall	0	0	1	0
Investigations	0	2	1	0
Blood pressure increased	0	2	0	0
Electrocardiogram QT prolonged	0	0	1	0
Nervous system disorders	1	3	0	1
Areflexia	0	1	0	0
Cerebral microhaemorrhage	1	1	0	1
Headache	0	1	0	0
Psychiatric disorders	0	1	1	1
Anxiety	0	0	0	1
Depression	0	1	0	1
Disorientation	0	0	1	0
Respiratory, thoracic and mediastinal disorders	1	0	0	0
Oropharyngeal discomfort	1	0	0	0
Vascular disorders	0	5	0	1
Hypertension	0	4	0	1
Orthostatic hypotension	0	1	0	0
Total preferred term events	2	14	3	8

Non serious AEs and SAEs are not separated out.
Subjects are counted only once per treatment in each row.
Includes all data collected since the first dose of study drug.
MedDRA (v14.1) coding dictionary applied.
AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; N= number of subjects in treatment group; n = number of subjects with specified criteria; SAE = serious adverse event; v = version.

Permanent Discontinuations due to Adverse Events: A total of 2 subjects discontinued from study treatment due to AEs; 1 subject (in the Cohort M PF-04360365 group) discontinued treatment due to an SAE of myocardial infarction, which was of moderate severity and not related to the study treatment. This subject remained in the study. One (1) subject (in the Cohort M placebo group) discontinued treatment due to an AE of cerebral microhemorrhage, which was of moderate severity and related to the study drug. This subject initially remained in the study, but later withdrew during the Follow-Up period due to no longer being willing to participate.

Dose Reductions or Temporary Discontinuations due to Adverse Events: One (1) subject in the Cohort Q, PF-04360365 group had a temporary discontinuation of study drug due to an AE of oropharyngeal discomfort, which was mild and related to the study drug. There were no dose reductions due to AEs.

Deaths: No deaths were reported during the study.

Other Safety Results: Clinician review of the vital sign data 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. There was no discernible pattern in ECG abnormalities, across the treatment groups. Neurological and 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. The most commonly observed brain MRI abnormality present at Baseline was mild white matter hyperintensity (range: 83.3% to 100%). There were no new clinically significant changes in brain MRI findings.

CONCLUSIONS:

- PF-04360365 was safe and well tolerated. No deaths were reported and the 4 SAEs reported were considered not related to study drug. There were 2 discontinuations of study drug due to AEs (myocardial infarction [Cohort M - PF-04360365 10 mg/kg loading dose and 7.5 mg/kg maintenance dose] and cerebral microhemorrhage {placebo}) and 1 temporary discontinuation of study drug due to an AE (oropharyngeal discomfort [Cohort Q - PF-04360365 10 mg/kg]).

- PF-04360365 exhibited dose-dependent increases in plasma concentrations, limited plasma accumulation, low CSF penetration, and was not detected in the urine.

- Robust increases from plasma Baseline concentrations observed for $A\beta_{1-x}$ and $A\beta_{1-40}$, while plasma $A\beta_{1-42}$ concentrations were highly variable and not quantifiable in the majority of subjects.

- The time course of CSF biomarkers did not appear to differ substantially for placebo- versus PF-04360365-treated subjects, nor was there any discernible dose response. $A\beta_{1-x}$ was not detected in the urine.

- No discernible differences in the percent change from Baseline in amyloid burden (as measured by [^{11}C] β-amyloid plaque imaging PET) were seen between the placebo and treatment arms for any individual brain region, or across brain regions.

- Serum anti-drug antibodies for PF-04360365 were not detected in any subjects in this study.

- At Month 13, the 90% CIs for the treatment differences for change from Baseline in ADAS-cog, DAD, and MMSE all overlapped 0.