



Clinical trial results:

A Phase 2, Randomized, Double-Blind Placebo Controlled Trial to Evaluate the Safety, Tolerability, Pharmacokinetics and Efficacy of PF-04360365 (Ponezumab) in Adult Subjects With Probable Cerebral Amyloid Angiopathy

Summary

EudraCT number	2013-001557-27
Trial protocol	GB NL
Global end of trial date	23 September 2015

Results information

Result version number	v1 (current)
This version publication date	30 September 2016
First version publication date	30 September 2016

Trial information

Trial identification

Sponsor protocol code	A9951024
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01821118
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Pfizer, Inc
Sponsor organisation address	235 E 42nd Street, New York, United States, 10017
Public contact	Pfizer ClinicalTrials.gov Call Center, Pfizer, Inc, 001 8007181021, ClinicalTrials.gov_Inquiries@pfizer.com
Scientific contact	Pfizer ClinicalTrials.gov Call Center, Pfizer, Inc, 001 8007181021, ClinicalTrials.gov_Inquiries@pfizer.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	23 September 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	23 September 2015
Global end of trial reached?	Yes
Global end of trial date	23 September 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Primary Objective: To evaluate the efficacy of PF-04360365 (ponezumab) in subjects with probable cerebral amyloid angiopathy (CAA) as compared to placebo on a blood oxygenation level dependent (BOLD) functional magnetic resonance imaging (fMRI) measure of cerebrovascular reactivity.

Secondary Objectives: To evaluate the efficacy of PF-04360365 (ponezumab) in subjects with probable CAA as compared to placebo on additional BOLD fMRI measures of cerebrovascular reactivity and to evaluate the effect of PF-04360365 (ponezumab) in subjects with probable CAA as compared to placebo on changes in the concentration of total plasma amyloid beta (AB).

Safety Objective: To evaluate the safety, tolerability and pharmacokinetics (PK) of PF-04360365 (ponezumab) in subjects with probable CAA.

Protection of trial subjects:

This study was conducted in compliance with the ethical principles originating in or derived from the Declaration of Helsinki and in compliance with all International Conference on Harmonization (ICH) Good Clinical Practice (GCP) Guidelines. In addition, all local regulatory requirements were followed; in particular, those affording greater protection to the safety of study subjects.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	25 June 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Canada: 5
Country: Number of subjects enrolled	France: 5
Country: Number of subjects enrolled	Netherlands: 2
Country: Number of subjects enrolled	United Kingdom: 4
Country: Number of subjects enrolled	United States: 20
Worldwide total number of subjects	36
EEA total number of subjects	11

Notes:

Subjects enrolled per age group

In utero	0
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Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	12
From 65 to 84 years	24
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

The study was conducted in 5 countries (Canada, France, Netherlands, United Kingdom, and United States). Male or female subjects of non childbearing potential between the ages of 55 and 80 years old were enrolled. Subjects must have had the diagnosis of probable CAA using the Modified Boston criteria.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Blinding implementation details:

Double-blind (subject and investigator blinded)

Arms

Are arms mutually exclusive?	Yes
Arm title	PF-04360365

Arm description:

Subjects received a loading dose of PF-04360365 10 milligrams (mg)/kilograms (kg) on Day 1, followed by PF-04360365 7.5 mg/kg on Days 30 and 60. PF-04360365 was administered via intravenous (IV) infusion over a period of 10-15 minutes (min) and dosing was based on subject weight.

Arm type	Experimental
Investigational medicinal product name	PF-04360365
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solvent for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

10 milligrams/kilograms (mg/kg) at Day 1, followed by 7.5 mg/kg at Days 30 and 60. Administered via intravenous (IV) infusion over a period of 10-15 minutes (mins).

Arm title	Placebo
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Arm description:

Subjects received a loading dose of placebo matching PF-04360365 10 mg/kg on Day 1, followed by placebo matching PF-04360365 7.5 mg/kg on Days 30 and 60. Placebo was also administered via IV infusion over a period of 10-15 min.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

10 mg/kg at Day 1, followed by 7.5 mg/kg at Days 30 and 60 administered via IV infusion over a period of 10-15 mins.

Number of subjects in period 1	PF-04360365	Placebo
Started	24	12
Completed	24	11
Not completed	0	1
Adverse event, serious fatal	-	1

Baseline characteristics

Reporting groups

Reporting group title	PF-04360365
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Reporting group description:

Subjects received a loading dose of PF-04360365 10 milligrams (mg)/kilograms (kg) on Day 1, followed by PF-04360365 7.5 mg/kg on Days 30 and 60. PF-04360365 was administered via intravenous (IV) infusion over a period of 10-15 minutes (min) and dosing was based on subject weight.

Reporting group title	Placebo
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Reporting group description:

Subjects received a loading dose of placebo matching PF-04360365 10 mg/kg on Day 1, followed by placebo matching PF-04360365 7.5 mg/kg on Days 30 and 60. Placebo was also administered via IV infusion over a period of 10-15 min.

Reporting group values	PF-04360365	Placebo	Total
Number of subjects	24	12	36
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	6	6	12
From 65-84 years	18	6	24
85 years and over	0	0	0
Age Continuous Units: years			
arithmetic mean	68.8	65	
standard deviation	± 6.8	± 5.7	-
Gender, Male/Female Units: participants			
Female	8	5	13
Male	16	7	23

End points

End points reporting groups

Reporting group title	PF-04360365
Reporting group description: Subjects received a loading dose of PF-04360365 10 milligrams (mg)/kilograms (kg) on Day 1, followed by PF-04360365 7.5 mg/kg on Days 30 and 60. PF-04360365 was administered via intravenous (IV) infusion over a period of 10-15 minutes (min) and dosing was based on subject weight.	
Reporting group title	Placebo
Reporting group description: Subjects received a loading dose of placebo matching PF-04360365 10 mg/kg on Day 1, followed by placebo matching PF-04360365 7.5 mg/kg on Days 30 and 60. Placebo was also administered via IV infusion over a period of 10-15 min.	

Primary: Change from baseline to Day 2 in cerebrovascular reactivity as measured by the slope (amplitude over time to peak) from visual task-evoked functional magnetic resonance imaging (fMRI)

End point title	Change from baseline to Day 2 in cerebrovascular reactivity as measured by the slope (amplitude over time to peak) from visual task-evoked functional magnetic resonance imaging (fMRI)
End point description: Blood Oxygen Level Dependant (BOLD) fMRI was performed at Screening (Baseline) and on Days 2 and 90. During each of these sessions, BOLD fMRI images were acquired in rapid succession as a flashing radial black and white checkerboard was presented alternately with a gray screen. This well established visual stimulus is known to produce a reliable increase in BOLD fMRI signal within the visual cortex region of the occipital lobe. The time course of the BOLD fMRI signal was used to assess the vascular reactivity. Imaging sites also acquired cerebral blood flow data using Arterial Spin Labeled (ASL) scans at Screening and on Days 2 and 90. A standard T1-weighted image was also acquired to aid image analysis. All efficacy scans were analyzed centrally. "n" signifies number of evaluable subjects for the specified region of interest (ROI) at Day 2. Geometric means are presented in original scale and standard errors (SE) are presented in natural logarithmic (log e) scale.	
End point type	Primary
End point timeframe: Baseline, Day 2	

End point values	PF-04360365	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	12		
Units: percent/second				
geometric mean (standard error)				
Region of interest (ROI) 1 (n=20, 11)	0.954 (± 0.085)	0.969 (± 0.073)		
ROI2 (n=23, 11)	0.933 (± 0.05)	0.999 (± 0.055)		

Statistical analyses

Statistical analysis title	ROI1 Day 2 geometric mean ratio
Statistical analysis description:	
Bayesian analysis of covariance (ANCOVA) model with treatment fitted as a fixed effect and baseline as a covariate, analyzed on a log e scale. Geometric mean ratio: PF-04360365/placebo.	
Comparison groups	PF-04360365 v Placebo
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	other ^[1]
Method	Bayesian ANCOVA
Parameter estimate	Geometric Mean Ratio
Point estimate	0.984
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.82
upper limit	1.184
Variability estimate	Standard error of the mean
Dispersion value	0.112

Notes:

[1] - SE of mean presented in log e scale.

Statistical analysis title	ROI2 Day 2 geometric mean ratio
Statistical analysis description:	
Bayesian ANCOVA model with treatment fitted as a fixed effect and baseline as a covariate, analyzed on a log e scale. Geometric mean ratio: PF-04360365/placebo.	
Comparison groups	PF-04360365 v Placebo
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	other ^[2]
Method	Bayesian ANCOVA
Parameter estimate	Geometric Mean Ratio
Point estimate	0.934
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.825
upper limit	1.056
Variability estimate	Standard error of the mean
Dispersion value	0.075

Notes:

[2] - SE of mean presented on log e scale.

Primary: Change from baseline to Day 90 in cerebrovascular reactivity as measured by the slope (amplitude over time to peak) from visual task-evoked fMRI

End point title	Change from baseline to Day 90 in cerebrovascular reactivity as measured by the slope (amplitude over time to peak) from visual task-evoked fMRI
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End point description:

BOLD fMRI was performed at Screening (Baseline) and on Days 2 and 90. During each of these sessions, BOLD fMRI images were acquired in rapid succession as a flashing radial black and white checkerboard was presented alternately with a gray screen. This well established visual stimulus is known to produce a reliable increase in BOLD fMRI signal within the visual cortex region of the occipital lobe. The time course of the BOLD fMRI signal was used to assess the vascular reactivity. Imaging sites also acquired

cerebral blood flow data using ASL scans at Screening and on Days 2 and 90. A standard T1-weighted image was also acquired to aid image analysis. All efficacy scans were analyzed centrally. "n" signifies number of evaluable subjects for the specified region of interest (ROI) at Day 90. Geometric means are presented in original scale and SEs are presented in log e scale.

End point type	Primary
End point timeframe:	
Baseline, Day 90	

End point values	PF-04360365	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	12		
Units: percent/second				
geometric mean (standard error)				
ROI1 (n=20, 10)	0.817 (\pm 0.064)	0.958 (\pm 0.063)		
ROI2 (n=23, 10)	0.857 (\pm 0.055)	0.95 (\pm 0.06)		

Statistical analyses

Statistical analysis title	ROI1 Day 90 geometric mean ratio
Statistical analysis description:	
Bayesian ANCOVA model with treatment fitted as a fixed effect and baseline as a covariate, analyzed on a log e scale. Geometric mean ratio: PF-03084014/placebo.	
Comparison groups	PF-04360365 v Placebo
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	other ^[3]
Method	Bayesian ANCOVA
Parameter estimate	Geometric Mean Ratio
Point estimate	0.852
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.735
upper limit	0.989
Variability estimate	Standard error of the mean
Dispersion value	0.091

Notes:

[3] - SE of mean presented on log e scale.

Statistical analysis title	ROI2 Day 90 geometric mean ratio
Statistical analysis description:	
Bayesian ANCOVA model with treatment fitted as a fixed effect and baseline as a covariate, analyzed on a log e scale. Geometric mean ratio: PF-03084014/placebo.	
Comparison groups	PF-04360365 v Placebo

Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	
Method	Bayesian ANCOVA
Parameter estimate	Geometric Mean Ratio
Point estimate	0.902
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.788
upper limit	1.031
Variability estimate	Standard error of the mean
Dispersion value	0.082

Secondary: Change from baseline to Day 2 and Day 90 in cerebrovascular reactivity as measured by the time to peak from visual task-evoked fMRI

End point title	Change from baseline to Day 2 and Day 90 in cerebrovascular reactivity as measured by the time to peak from visual task-evoked fMRI
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End point description:

BOLD fMRI was performed at Screening (Baseline) and on Days 2 and 90. During each of these sessions, BOLD fMRI images were acquired in rapid succession as a flashing radial black and white checkerboard was presented alternately with a gray screen. This well established visual stimulus is known to produce a reliable increase in BOLD fMRI signal within the visual cortex region of the occipital lobe. The time course of the BOLD fMRI signal was used to assess the vascular reactivity. Imaging sites also acquired cerebral blood flow data using ASL scans at Screening and on Days 2 and 90. A standard T1-weighted image was also acquired to aid image analysis. All efficacy scans were analyzed centrally. "n" signifies number of evaluable subjects for the specified ROI at the specified days. Geometric means are presented in original scale and SEs are presented in log e scale.

End point type	Secondary
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End point timeframe:

Baseline, Day 2, Day 90

End point values	PF-04360365	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	12		
Units: seconds				
geometric mean (standard error)				
ROI1, Day 2 (n=20, 11)	1.012 (± 0.028)	1.007 (± 0.037)		
ROI1, Day 90 (n=20, 10)	1.065 (± 0.02)	1.015 (± 0.03)		
ROI2, Day 2 (n=23, 11)	1.008 (± 0.018)	1.01 (± 0.026)		
ROI2, Day 90 (n=23, 10)	1.039 (± 0.018)	1.028 (± 0.026)		

Statistical analyses

Statistical analysis title	ROI1 Day 2 geometric mean ratio
Statistical analysis description: Bayesian ANCOVA model with treatment fitted as a fixed effect and baseline as a covariate, analyzed on a log e scale. Geometric mean ratio: PF-03084014/placebo.	
Comparison groups	PF-04360365 v Placebo
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	other ^[4]
Method	Bayesian ANCOVA
Parameter estimate	Geometric Mean Ratio
Point estimate	1.005
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.933
upper limit	1.086
Variability estimate	Standard error of the mean
Dispersion value	0.046

Notes:

[4] - SE of mean presented on log e scale.

Statistical analysis title	ROI1 Day 90 geometric mean ratio
Statistical analysis description: Bayesian ANCOVA model with treatment fitted as a fixed effect and baseline as a covariate, analyzed on a log e scale. Geometric mean ratio: PF-03084014/placebo.	
Comparison groups	PF-04360365 v Placebo
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	other ^[5]
Method	Bayesian ANCOVA
Parameter estimate	Geometric Mean Ratio
Point estimate	1.049
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.99
upper limit	1.114
Variability estimate	Standard error of the mean
Dispersion value	0.036

Notes:

[5] - SE of mean presented on log e scale.

Statistical analysis title	ROI2 Day 2 geometric mean ratio
Statistical analysis description: Bayesian ANCOVA model with treatment fitted as a fixed effect and baseline as a covariate, analyzed on a log e scale. Geometric mean ratio: PF-03084014/placebo.	
Comparison groups	PF-04360365 v Placebo

Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	other ^[6]
Method	Bayesian ANCOVA
Parameter estimate	Geometric Mean Ratio
Point estimate	0.998
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.947
upper limit	1.052
Variability estimate	Standard error of the mean
Dispersion value	0.032

Notes:

[6] - SE of mean presented on log e scale.

Statistical analysis title	ROI2 Day 90 geometric mean ratio
Statistical analysis description:	
Bayesian ANCOVA model with treatment fitted as a fixed effect and baseline as a covariate, analyzed on a log e scale. Geometric mean ratio: PF-03084014/placebo.	
Comparison groups	PF-04360365 v Placebo
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	other ^[7]
Method	Bayesian ANCOVA
Parameter estimate	Geometric Mean Ratio
Point estimate	1.01
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.96
upper limit	1.063
Variability estimate	Standard error of the mean
Dispersion value	0.031

Notes:

[7] - SE of mean presented on log e scale.

Secondary: Change from baseline to Day 2 and Day 90 in cerebrovascular reactivity as measured by the amplitude from visual task-evoked fMRI

End point title	Change from baseline to Day 2 and Day 90 in cerebrovascular reactivity as measured by the amplitude from visual task-evoked fMRI
End point description:	
BOLD fMRI was performed at Screening (Baseline) and on Days 2 and 90. During each of these sessions, BOLD fMRI images were acquired in rapid succession as a flashing radial black and white checkerboard was presented alternately with a gray screen. This well established visual stimulus is known to produce a reliable increase in BOLD fMRI signal within the visual cortex region of the occipital lobe. The time course of the BOLD fMRI signal was used to assess the vascular reactivity. Imaging sites also acquired cerebral blood flow data using ASL scans at Screening and on Days 2 and 90. A standard T1-weighted image was also acquired to aid image analysis. All efficacy scans were analyzed centrally. "n" signifies number of evaluable subjects for the specified ROI at the specified days. All values presented are on log e scale.	
End point type	Secondary

End point timeframe:
Baseline, Day 2, Day 90

End point values	PF-04360365	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	12		
Units: percent				
least squares mean (confidence interval 90%)				
ROI1, Day 2 (n=20, 11)	-0.0381 (-0.1655 to 0.0894)	-0.0983 (-0.2715 to 0.075)		
ROI1, Day 90 (n=20, 10)	-0.1389 (-0.2513 to -0.0264)	-0.053 (-0.2135 to 0.1075)		
ROI2, Day 2 (n=23, 11)	-0.0714 (-0.1584 to 0.0156)	-0.0226 (-0.1484 to 0.1033)		
ROI2, Day 90 (n=23, 10)	-0.1245 (-0.2236 to -0.0254)	-0.0357 (-0.1861 to 0.1146)		

Statistical analyses

Statistical analysis title	ROI1 Day 2 geometric mean ratio
Statistical analysis description: ANCOVA model with log e (baseline value) as a covariate, analyzed on log e scale. Geometric mean ratio: PF-03084014/placebo.	
Comparison groups	PF-04360365 v Placebo
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	other
Method	ANCOVA
Parameter estimate	Estimated Treatment Difference (log e)
Point estimate	0.0602
Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.1576
upper limit	0.2781
Variability estimate	Standard error of the mean
Dispersion value	0.1281

Statistical analysis title	ROI1 Day 90 geometric mean ratio
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Statistical analysis description:

ANCOVA model with log e (baseline value) as a covariate, analyzed on log e scale. Geometric mean ratio: PF-03084014/placebo.

Comparison groups	PF-04360365 v Placebo
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	other
Method	ANCOVA
Parameter estimate	Estimated Treatment Difference (log e)
Point estimate	-0.0859
Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.2843
upper limit	0.1124
Variability estimate	Standard error of the mean
Dispersion value	0.1165

Statistical analysis title	ROI2 Day 2 geometric mean ratio
Statistical analysis description: ANCOVA model with log e (baseline value) as a covariate, analyzed on log e scale. Geometric mean ratio: PF-03084014/placebo.	
Comparison groups	PF-04360365 v Placebo
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	other
Method	ANCOVA
Parameter estimate	Estimated Treatment Difference (log e)
Point estimate	-0.0488
Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.2018
upper limit	0.1042
Variability estimate	Standard error of the mean
Dispersion value	0.0902

Statistical analysis title	ROI2 Day 90 geometric mean ratio
Statistical analysis description: ANCOVA model with log e (baseline value) as a covariate, analyzed on log e scale. Geometric mean ratio: PF-03084014/placebo.	
Comparison groups	PF-04360365 v Placebo
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	other
Method	ANCOVA
Parameter estimate	Estimated Treatment Difference (log e)
Point estimate	-0.0888

Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.2689
upper limit	0.0914
Variability estimate	Standard error of the mean
Dispersion value	0.1061

Secondary: Change from baseline to Day 2 and Day 90 in cerebrovascular reactivity as measured by the time to return to baseline from visual task-evoked fMRI

End point title	Change from baseline to Day 2 and Day 90 in cerebrovascular reactivity as measured by the time to return to baseline from visual task-evoked fMRI
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End point description:

BOLD fMRI was performed at Screening (Baseline) and on Days 2 and 90. During each of these sessions, BOLD fMRI images were acquired in rapid succession as a flashing radial black and white checkerboard was presented alternately with a gray screen. This well established visual stimulus is known to produce a reliable increase in BOLD fMRI signal within the visual cortex region of the occipital lobe. The time course of the BOLD fMRI signal was used to assess the vascular reactivity. Imaging sites also acquired cerebral blood flow data using ASL scans at Screening and on Days 2 and 90. A standard T1-weighted image was also acquired to aid image analysis. All efficacy scans were analyzed centrally. "n" signifies number of evaluable subjects for the specified ROI at the specified days. All values presented are on log e scale.

End point type	Secondary
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End point timeframe:

Baseline, Day 2, Day 90

End point values	PF-04360365	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	12		
Units: seconds				
least squares mean (confidence interval 90%)				
ROI1, Day 2 (n=20, 11)	0.0245 (-0.0155 to 0.0644)	-0.022 (-0.0759 to 0.0319)		
ROI1, Day 90 (n=20, 10)	0.0558 (0.0182 to 0.0934)	-0.0179 (-0.0711 to 0.0354)		
ROI2, Day 2 (n=23, 11)	0.0045 (-0.028 to 0.0369)	-0.0174 (-0.0643 to 0.0295)		
ROI2, Day 90 (n=23, 10)	0.0275 (-0.004 to 0.0589)	0.0158 (-0.0322 to 0.0637)		

Statistical analyses

Statistical analysis title	ROI1 Day 2 geometric mean ratio
Statistical analysis description: ANCOVA model with log e (baseline value) as a covariate, analyzed on a log e scale. Geometric mean ratio: PF-03084014/placebo.	
Comparison groups	PF-04360365 v Placebo
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	other
Method	ANCOVA
Parameter estimate	Estimated Treatment Difference (log e)
Point estimate	0.0464
Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.0207
upper limit	0.1136
Variability estimate	Standard error of the mean
Dispersion value	0.0395

Statistical analysis title	ROI2 Day 2 geometric mean ratio
Statistical analysis description: ANCOVA model with log e (baseline value) as a covariate, analyzed on a log e scale. Geometric mean ratio: PF-03084014/placebo.	
Comparison groups	PF-04360365 v Placebo
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	other
Method	ANCOVA
Parameter estimate	Estimated Treatment Difference (log e)
Point estimate	0.0219
Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.0352
upper limit	0.079
Variability estimate	Standard error of the mean
Dispersion value	0.0337

Statistical analysis title	ROI1 Day 90 geometric mean ratio
Statistical analysis description: ANCOVA model with log e (baseline value) as a covariate, analyzed on a log e scale. Geometric mean ratio: PF-03084014/placebo.	
Comparison groups	PF-04360365 v Placebo

Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	other
Method	ANCOVA
Parameter estimate	Estimated Treatment Difference (log e)
Point estimate	0.0737
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.0084
upper limit	0.139
Variability estimate	Standard error of the mean
Dispersion value	0.0383

Statistical analysis title	ROI2 Day 90 geometric mean ratio
Statistical analysis description: ANCOVA model with log e (baseline value) as a covariate, analyzed on a log e scale. Geometric mean ratio: PF-03084014/placebo.	
Comparison groups	PF-04360365 v Placebo
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	other
Method	ANCOVA
Parameter estimate	Estimated Treatment Difference (log e)
Point estimate	0.0117
Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.046
upper limit	0.0694
Variability estimate	Standard error of the mean
Dispersion value	0.034

Secondary: Change from baseline in concentration of total plasma amyloid beta (AB)

End point title	Change from baseline in concentration of total plasma amyloid beta (AB)
End point description: Cerebral amyloid angiopathy (CAA) is caused by the progressive deposition of amyloid, predominantly AB40, within the walls of cerebral blood vessels with a predisposition for the vessels of the occipital lobe. As such, it is of interest to investigate the effect of PF-04360365 on AB concentrations. AB1-x and AB1-40 were investigated. "n" signifies number of subjects with measurable AB at the specified time point.	
End point type	Secondary
End point timeframe: Day 1 (pre dose and 8 hours post dose), Day 2, Day 30, Day 90, Day 240 (or at Early Termination)	

End point values	PF-04360365	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	12		
Units: picograms (pg)/milliliter (mL)				
arithmetic mean (standard deviation)				
AB1-x, Day 1 (n=4, 3)	4374 (± 420.62)	5.3 (± 26.01)		
AB1-x, Day 2 (n=4, 3)	13911.8 (± 3292.88)	-37.7 (± 29.02)		
AB1-x, Day 30 (n=4, 3)	94468.5 (± 11946.21)	-48.3 (± 103.32)		
AB1-x, Day 90 (n=4, 2)	111312.8 (± 24677.74)	-62 (± 141.42)		
AB1-x, Day 240 (n=4, 3)	30495.8 (± 10931.16)	13 (± 116.76)		
AB1-40, Day 1 (n=23, 11)	4747.6 (± 1039.96)	-8.4 (± 30.08)		
AB1-40, Day 2 (n=23, 11)	12845.2 (± 2887.91)	0.5 (± 30.9)		
AB1-40, Day 30 (n=23, 10)	68010.1 (± 17396.04)	-5 (± 46.81)		
AB1-40, Day 90 (n=23, 10)	87710.8 (± 18699.28)	0.7 (± 44.02)		
AB1-40, Day 240 (n=23, 9)	20665.6 (± 7132.91)	-6.2 (± 35.63)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with brain structural magnetic resonance imaging (sMRI) abnormalities

End point title	Number of subjects with brain structural magnetic resonance imaging (sMRI) abnormalities
End point description:	
Brain sMRI abnormalities included cerebral edema and total infarcts (including cortical infarcts, white matter infarcts, and subcortical gray matter infarcts). "Total infarcts" is the total number of subjects with at least 1 type of infarct.	
End point type	Secondary
End point timeframe:	
Baseline/Screening, Day 15, Day 45, Day 90.	

End point values	PF-04360365	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	12		
Units: subjects				
Cerebral edema, Screening	0	1		
Cerebral edema, Day 15	0	1		
Cerebral edema, Day 45	0	1		
Cerebral edema, Day 90	1	1		

Total infarcts, Screening	5	3		
Total infarcts, Day 15	5	3		
Total infarcts, Day 45	5	3		
Total infarcts, Day 90	5	3		
Cortical infarcts, Screening	0	0		
Cortical infarcts, Day 15	0	0		
Cortical infarcts, Day 45	0	0		
Cortical infarcts, Day 90	0	0		
White matter infarcts, Screening	3	2		
White matter infarcts, Day 15	3	2		
White matter infarcts, Day 45	3	2		
White matter infarcts, Day 90	3	2		
Subcortical gray matter infarcts, Screening	3	1		
Subcortical gray matter infarcts, Day 15	3	1		
Subcortical gray matter infarcts, Day 45	3	1		
Subcortical gray matter infarcts, Day 90	3	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Montreal Cognitive Assessment (MoCA) Total Score Over Time

End point title	Mean Montreal Cognitive Assessment (MoCA) Total Score Over Time
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End point description:

The Montreal Cognitive Assessment (MoCA) was used as a safety outcome measure to assess any changes in cognition. The MoCA is a 1-page 30-point test administered in approximately 10 minutes. The MoCA assessed short term memory, visuospatial abilities, multiple aspects of executive functions, attention, concentration, working memory, and language, as well as orientation to time and place. A score of more than or equal to (\geq) 26 to 30 (maximum possible point) is considered as normal. An average of 22 points is considered as mild cognitive impairment. Lower scores indicate decreasing cognitive function. On Day 240, the number of evaluable participants in the placebo group was 11 instead of 12.

End point type	Secondary
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End point timeframe:

Screening; Days 0, 1, 30, 60, 90, and 240

End point values	PF-04360365	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	12		
Units: units on a scale				
arithmetic mean (standard deviation)				
Screening	25.4 (\pm 4.24)	25.9 (\pm 1.73)		
Day 0	25.5 (\pm 3.41)	25.9 (\pm 3.34)		
Day 1	25.1 (\pm 3.1)	25.8 (\pm 2.73)		
Day 30	27 (\pm 2.46)	26.8 (\pm 2.53)		
Day 60	26.6 (\pm 3.12)	26.8 (\pm 3.33)		
Day 90	26 (\pm 3.46)	26.7 (\pm 3.14)		

Day 240	26.1 (\pm 3.43)	26.5 (\pm 2.73)		
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Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with all causality and treatment-related treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), and discontinuations due to adverse events (AEs)

End point title	Number of subjects with all causality and treatment-related treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), and discontinuations due to adverse events (AEs)
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End point description:

An AE was any untoward medical occurrence attributed to study drug in a subject who received study drug. AEs comprised both SAEs and non-SAEs. An SAE was an AE resulting in any of the following outcomes or deemed significant for any other reason: death; initial or prolonged inpatient hospitalization; life-threatening experience (immediate risk of dying); persistent or significant disability/incapacity; congenital anomaly. Treatment-emergent adverse events (TEAEs) were defined as newly occurring AEs or those worsening after first dose.

End point type	Secondary
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End point timeframe:

Baseline up to Day 240

End point values	PF-04360365	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	12		
Units: subjects				
All causality TEAEs	16	8		
Treatment-related TEAEs	2	2		
All causality SAEs	2	2		
Treatment-related SAEs	0	1		
All causality severe TEAEs	2	2		
Treatment-related severe TEAEs	0	1		
Discontinued due to all causality TEAEs	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with laboratory abnormalities

End point title	Number of subjects with laboratory abnormalities
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End point description:

Number of subjects with laboratory test abnormalities without regard to baseline abnormality.

Laboratory test parameters included hematology, liver function (including Hy's Law Criteria), renal function, electrolytes, clinical chemistry, and urinalysis (dipstick and microscopy).

End point type	Secondary
End point timeframe:	
Baseline up to Day 240	

End point values	PF-04360365	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	12		
Units: subjects	14	10		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with vital signs values meeting categorical summarization criteria

End point title	Number of subjects with vital signs values meeting categorical summarization criteria
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End point description:

Categorical summarization criteria in vital signs included: supine systolic blood pressure (SBP) of less than (<)90 millimeters of mercury (mm Hg) or more than (>) 160 mm Hg; supine diastolic blood pressure (DBP) <50 mm Hg or >100 mm Hg; supine pulse rate of <60 beats per minute (bpm) or >100 bpm; maximum changes (increase or decrease) from baseline in supine SBP of ≥ 20 mm Hg; maximum increase from baseline in supine DBP of ≥ 20 mm Hg; and maximum decrease from baseline in supine DBP of ≥ 10 mm Hg.

End point type	Secondary
End point timeframe:	
Baseline up to Day 240	

End point values	PF-04360365	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	12		
Units: subjects				
Supine SBP <90 mm Hg	1	0		
Supine SBP >160 mm Hg	2	2		
Supine DBP <50 mm Hg	1	0		
Supine DBP >100 mm Hg	0	1		
Supine pulse rate <60 bpm	16	7		
Supine pulse rate >100 bpm	0	1		
Increase from baseline in supine SBP ≥ 20 mm Hg	6	4		
Increase from baseline in supine DBP ≥ 20 mm Hg	1	1		
Decrease from baseline in supine SBP ≥ 20 mm Hg	9	6		

Decrease from baseline in supine DBP ≥10 mm Hg	13	5		
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Statistical analyses

No statistical analyses for this end point

Secondary: Overall number of subjects with positive responses to questions on the Columbia Suicide Severity Rating Scale (C-SSRS)

End point title	Overall number of subjects with positive responses to questions on the Columbia Suicide Severity Rating Scale (C-SSRS)
End point description: C-SSRS assessed whether subject responded "yes" to the following: completed suicide, suicide attempt, preparatory acts toward imminent suicidal behavior, suicidal ideation, self-injurious behavior with no suicidal intent.	
End point type	Secondary
End point timeframe: Baseline up to Day 240	

End point values	PF-04360365	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	12		
Units: subjects				
Completed suicide	0	0		
Suicide attempt	0	0		
Preparatory acts to imminent suicidal behaviour	0	0		
Self-injurious behaviour, no suicidal intent	1	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with significant changes from baseline in physical examination at final visit

End point title	Number of subjects with significant changes from baseline in physical examination at final visit
End point description: A complete physical examination included head, ears, eyes, nose, mouth, skin, heart and lung examinations, lymph nodes, gastrointestinal, skeletal, and neurological systems.	
End point type	Secondary
End point timeframe: Baseline up to Final Visit (Day 240)	

End point values	PF-04360365	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	12		
Units: subjects	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with significant changes in neurological examination results

End point title	Number of subjects with significant changes in neurological examination results
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End point description:

A complete/full neurological examination included assessment of the cranial nerves; muscle strength, tone, cortical drift, abnormal movements; deep tendon reflexes; sensory exam, coordination, gait and station.

End point type	Secondary
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End point timeframe:

Baseline up till Day 240

End point values	PF-04360365	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	12		
Units: subjects	2	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with anti-PF-04360365 antibodies

End point title	Number of subjects with anti-PF-04360365 antibodies ^[8]
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End point description:

Blood samples were collected from subjects who received active treatment to assess for presence/absence of anti-PF-04360365 antibodies.

End point type	Secondary
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End point timeframe:

Day 1 up to Day 240

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Statistical Analysis was not performed for this endpoint

End point values	PF-04360365			
Subject group type	Reporting group			
Number of subjects analysed	24			
Units: subjects	0			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events (AEs) and serious AEs (SAEs) monitoring started from screening through and including 28 calendar days after the last administration of the investigational product.

Adverse event reporting additional description:

All treated subjects were analyzed for AEs. The same event may appear as both an AE and an SAE. However, what is presented are distinct events. An event may be categorized as serious in one subject and as nonserious in another subject, or one subject may have experienced both a serious and a nonserious event during the study.

Assessment type	Non-systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	18.1
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Reporting groups

Reporting group title	Placebo
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Reporting group description:

Subjects received a loading dose of placebo matching PF-04360365 10 mg/kg at Day 1, followed by placebo matching PF-04360365 7.5 mg/kg at Days 30 and 60. Placebo was also administered via IV infusion over a period of 10-15 min.

Reporting group title	PF-04360365
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Reporting group description:

Subjects received a loading dose of PF-04360365 10 milligrams (mg)/kilograms (kg) at Day 1, followed by PF-04360365 7.5 mg/kg at Days 30 and 60. PF-04360365 was administered via intravenous (IV) infusion over a period of 10-15 minutes (min) and dosing was based on subject weight.

Serious adverse events	Placebo	PF-04360365	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 12 (16.67%)	2 / 24 (8.33%)	
number of deaths (all causes)	1	0	
number of deaths resulting from adverse events	1	0	
Injury, poisoning and procedural complications			
Subdural haematoma			
subjects affected / exposed	0 / 12 (0.00%)	1 / 24 (4.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Aphasia			
subjects affected / exposed	0 / 12 (0.00%)	1 / 24 (4.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral haemorrhage			

subjects affected / exposed	0 / 12 (0.00%)	1 / 24 (4.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage intracranial			
subjects affected / exposed	1 / 12 (8.33%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Migraine with aura			
subjects affected / exposed	1 / 12 (8.33%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Placebo	PF-04360365	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	8 / 12 (66.67%)	16 / 24 (66.67%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Squamous cell carcinoma			
subjects affected / exposed	0 / 12 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	1 / 12 (8.33%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Fatigue			
subjects affected / exposed	0 / 12 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	1	
Gait disturbance			
subjects affected / exposed	0 / 12 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	1	
Immune system disorders			
Hypersensitivity			

subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	1 / 24 (4.17%) 1	
Reproductive system and breast disorders Testicular cyst subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	1 / 24 (4.17%) 1	
Respiratory, thoracic and mediastinal disorders Oropharyngeal pain subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1	0 / 24 (0.00%) 0	
Psychiatric disorders Depression subjects affected / exposed occurrences (all) Emotional disorder subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 2 0 / 12 (0.00%) 0	0 / 24 (0.00%) 0 1 / 24 (4.17%) 1	
Investigations Haemoglobin decreased subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	1 / 24 (4.17%) 1	
Injury, poisoning and procedural complications Fall subjects affected / exposed occurrences (all) Jaw fracture subjects affected / exposed occurrences (all) Road traffic accident subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0 0 / 12 (0.00%) 0 0 / 12 (0.00%) 0	2 / 24 (8.33%) 3 1 / 24 (4.17%) 1 1 / 24 (4.17%) 1	
Cardiac disorders Palpitations subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	1 / 24 (4.17%) 1	
Nervous system disorders			

Aphasia			
subjects affected / exposed	1 / 12 (8.33%)	1 / 24 (4.17%)	
occurrences (all)	1	1	
Balance disorder			
subjects affected / exposed	0 / 12 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	2	
Cerebellar syndrome			
subjects affected / exposed	0 / 12 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	1	
Cerebrovascular accident			
subjects affected / exposed	0 / 12 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	1	
Coordination abnormal			
subjects affected / exposed	0 / 12 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	1	
Dizziness			
subjects affected / exposed	0 / 12 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	1	
Epilepsy			
subjects affected / exposed	1 / 12 (8.33%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Headache			
subjects affected / exposed	1 / 12 (8.33%)	3 / 24 (12.50%)	
occurrences (all)	1	3	
Hypoaesthesia			
subjects affected / exposed	1 / 12 (8.33%)	1 / 24 (4.17%)	
occurrences (all)	1	1	
Migraine			
subjects affected / exposed	0 / 12 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	1	
Paraesthesia			
subjects affected / exposed	1 / 12 (8.33%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Partial seizures			
subjects affected / exposed	1 / 12 (8.33%)	0 / 24 (0.00%)	
occurrences (all)	1	0	

Presyncope subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	1 / 24 (4.17%) 1	
Superficial siderosis of central nervous system subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1	0 / 24 (0.00%) 0	
Eye disorders			
Dry eye subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	1 / 24 (4.17%) 1	
Vitreous floaters subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	1 / 24 (4.17%) 1	
Gastrointestinal disorders			
Constipation subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	1 / 24 (4.17%) 1	
Diarrhoea subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	1 / 24 (4.17%) 1	
Paraesthesia oral subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1	0 / 24 (0.00%) 0	
Toothache subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1	0 / 24 (0.00%) 0	
Vomiting subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	1 / 24 (4.17%) 1	
Skin and subcutaneous tissue disorders			
Alopecia subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1	0 / 24 (0.00%) 0	
Eczema subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	1 / 24 (4.17%) 1	

Pruritus			
subjects affected / exposed	1 / 12 (8.33%)	1 / 24 (4.17%)	
occurrences (all)	1	1	
Rash			
subjects affected / exposed	1 / 12 (8.33%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Rash macular			
subjects affected / exposed	0 / 12 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 12 (8.33%)	2 / 24 (8.33%)	
occurrences (all)	1	2	
Neck pain			
subjects affected / exposed	0 / 12 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	1	
Infections and infestations			
Fungal skin infection			
subjects affected / exposed	0 / 12 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	1	
Influenza			
subjects affected / exposed	0 / 12 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	1	
Nasopharyngitis			
subjects affected / exposed	0 / 12 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	1	
Sinusitis			
subjects affected / exposed	1 / 12 (8.33%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Upper respiratory tract infection			
subjects affected / exposed	0 / 12 (0.00%)	3 / 24 (12.50%)	
occurrences (all)	0	3	
Urinary tract infection			
subjects affected / exposed	2 / 12 (16.67%)	0 / 24 (0.00%)	
occurrences (all)	2	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 December 2012	Inclusion/exclusion criteria updated and other minor updates/clarifications
23 July 2013	Minor wording updates/changes
09 April 2014	Acknowledge safety and tolerability profile in the protocol is in line with past Alzheimer's Disease studies; updated exclusion criteria related to seizure history, body weight, and use of anti-epileptic drugs; Other clarifications and updates to reflect the updated protocol template.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported