Clinical trial results:
A Randomized, 18-Week, Placebo-Controlled, Double Blind, Parallel Group Study of the Safety and Efficacy of PF-05212377 (SAM-760) in Subjects With Mild to-Moderate Alzheimer's Disease With Existing Neuropsychiatric Symptoms on a Stable Daily Dose of Donepezil

Summary

EudraCT number	2014-000830-42
Trial protocol	ES GB
Global end of trial date	15 September 2015

Results information

Result version number	v1
This version publication date	11 September 2016
First version publication date	11 September 2016

Trial information

Trial identification

Sponsor protocol code	B2081011

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
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, Inc., Pfizer, Inc., 001 800-718-1021, ClinicalTrials.gov_Inquiries@pfizer.com
Scientific contact	Pfizer, Inc., Pfizer, Inc., 001 800-718-1021, 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	17 May 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	15 September 2015
Global end of trial reached?	Yes
Global end of trial date	15 September 2015
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

Primary Objective:
To evaluate the efficacy of PF-05212377 (SAM 760) 30 milligram (mg) once daily (QD) as compared to placebo on the primary measure of cognition and memory, the Alzheimer's Disease Assessment Scale cognitive subscale 13 item version (ADAS-cog13) 12 weeks after start of double blind study medication.

Secondary Objective:
To evaluate the efficacy of PF-05212377 30 mg QD as compared to placebo on a broad measure of behavior, the Neuropsychiatric Inventory (NPI) (12 item) at 12 weeks after start of double blind study medication.

Protection of trial subjects:

This study was conducted in compliance with good clinical practice (GCP) guidelines and, where applicable, local country regulations relevant to the use of new therapeutic agents in the country/countries of conduct, including the archiving of essential documents.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	14 November 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 12
Country: Number of subjects enrolled	Spain: 1
Country: Number of subjects enrolled	Chile: 39
Country: Number of subjects enrolled	United Kingdom: 2
Country: Number of subjects enrolled	United States: 125
Country: Number of subjects enrolled	Canada: 16
Worldwide total number of subjects	195
EEA total number of subjects	15

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
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)	15
From 65 to 84 years	151
85 years and over	29

Subject disposition

Recruitment

Recruitment details:

This study was a multicenter Phase 2a, randomized, placebo controlled, safety and efficacy study of 18 weeks in duration in subjects with mild-to-moderate Alzheimer's disease (AD) who were stable on treatment with 5 or 10 mg of donepezil and who had existing neuropsychiatric symptoms.

Pre-assignment

Screening details:

Before entering in the 12-week treatment period, participants were required to enter a 4-week placebo run-in period. 195 participants started the run-in period, of which 185 were eligible for the treatment period. One subject who discontinued during the placebo run-in was incorrectly enrolled into the double-blind period but was never treated.

Period 1

Period 1 title	Placebo Run-in Period
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Single blind
Roles blinded	Subject

Arms

Arm title	Placebo Run-in Period

Arm description:

All subjects receiving placebo during the single-blind placebo run-in period

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Placebo was administered as capsule once daily in the morning.

Number of subjects in period 1	Placebo Run-in Period
Started	195
Completed	185
Not completed	10
Adverse event, non-fatal	2
No longer willing to participate in study	1
No longer met eligibility criteria	5
Unspecified	1
Lost to follow-up	1

Period 2

Period 2 title	Double-blind treatment period
Is this the baseline period?	Yes[1]
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	PF-05212377 30 mg

Arm description:

All subjects receiving PF-05212377 30 mg during double blind period.

Arm type	Experimental
Investigational medicinal product name	PF-05212377
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

PF-05212377 was provided as 15 mg capsules once daily in the morning

Arm title	Placebo

Arm description:

All subjects receiving placebo during the double blind period

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Placebo was administered as capsule once daily in the morning.

Notes:

[1] - Period 1 is not the baseline period. It is expected that period 1 will be the baseline period.

Justification: Period 1 for this study is considered the placebo run-in period

Number of subjects in period 2[2]	PF-05212377 30 mg	Placebo
Started	91	94
Completed	77	86
Not completed	15	8
Adverse event, serious fatal	1	-
Adverse event, non-fatal	2	1
No longer meets eligibility criteria	3	-
Randomized but not treated	1	-
No longer willing to participate in study	2	4

Unspecified	4	1
Lost to follow-up	2	1
Protocol deviation	-	1
Joined	1	0
Randomized but not treated	1	-

Notes:

[2] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: The worldwide number enrolled in the trial includes all subjects included for safety reporting and enrolled in the placebo run-in period

Baseline characteristics

Reporting groups

Reporting group title	Double-blind treatment period

Reporting group description: -

Reporting group values	Double-blind treatment period	Total	
Number of subjects	186	186	
Age Categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	14	14	
From 65-84 years	144	144	
85 years and over	28	28	
Age Continuous Units: years			
arithmetic mean	76		
standard deviation	± 7.7	-	
Gender Categorical Units: Subjects			
Female	101	101	
Male	85	85	

End points

End points reporting groups

Reporting group title	Placebo Run-in Period
Reporting group description:	
All subjects receiving placebo during the single-blind placebo run-in period	
Reporting group title	PF-05212377 30 mg
Reporting group description:	
All subjects receiving PF-05212377 30 mg during double blind period.	
Reporting group title	Placebo
Reporting group description:	
All subjects receiving placebo during the double blind period	

Primary: Change From Baseline in ADAS-cog13 Total Score at Week 16

End point title	Change From Baseline in ADAS-cog13 Total Score at Week 16
End point description:	
ADAS-cog13 (13-item ADAS cog) is a psychometric instrument that evaluates word recall, ability to follow commands,constructional praxis, naming, ideational praxis, orientation, word recognition, memory, comprehension of spoken language, word-finding, and language ability, with a measure of delayed word recall and concentration/ distractibility. The total score of the 13-item scale ranges from 0 to 85, with an increase in score indicating cognitive worsening. The Full Analysis Set (FAS) is defined as all subjects who were randomized. The FAS was the primary analysis set for efficacy data.	
End point type	Primary
End point timeframe:	
Baseline (Visit 2, Week 4) and Week 16 (Visit 5)	

End point values	PF-05212377 30 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	78	86		
Units: scores on a scale				
least squares mean (standard error)	0.111 (± 0.629)	-0.584 (± 0.5995)		

Statistical analyses

Statistical analysis title	Difference between PF-05212377 30 mg and placebo
Statistical analysis description:	
Mixed Models Analysis	
Comparison groups	PF-05212377 30 mg v Placebo

Number of subjects included in analysis	164
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Mean difference (net)
Point estimate	0.695
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-0.424
upper limit	1.814
Variability estimate	Standard error of the mean
Dispersion value	0.8697

Secondary: Change From Baseline in the Neuropsychiatric Inventory (NPI) Total Score at Week 16

End point title	Change From Baseline in the Neuropsychiatric Inventory (NPI) Total Score at Week 16

End point description:

The NPI evaluates both frequency and severity of 12 neuropsychiatric disturbances including delusions, hallucinations, agitation/aggression, depression/dysphoria, anxiety, elation/euphoria, apathy/indifference, disinhibition, irritability/lability, motor disturbance, nighttime behaviors, as well as appetite/eating. The NPI total score (for 12 behavioral domains) is calculated as the product of frequency and severity for each domain, and ranges from 0 to 144. An increase in score indicates a worsening of symptoms. The FAS is defined as all subjects who are randomized. The FAS was the primary analysis set for efficacy data.

End point type	Secondary

End point timeframe:

Baseline (Visit 2, Week 4) and Week 16 (Visit 5)

End point values	PF-05212377 30 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	78	87		
Units: scores on scale				
least squares mean (standard error)	-3.99 (± 1.2441)	-6.184 (± 1.1801)		

Statistical analyses

Statistical analysis title	Difference between PF-05212377 30 mg and placebo

Statistical analysis description:

Mixed Models Analysis

Comparison groups	PF-05212377 30 mg v Placebo

Number of subjects included in analysis	165
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Median difference (net)
Point estimate	2.194
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-0.013
upper limit	4.401
Variability estimate	Standard error of the mean
Dispersion value	1.7149

Other pre-specified: Percentage of Subjects with Treatment Emergent Adverse Events (TEAEs) Leading to Discontinuation

End point title	Percentage of Subjects with Treatment Emergent Adverse Events (TEAEs) Leading to Discontinuation

End point description:

Proportion (%) of subjects with TEAEs leading to discontinuation over the 12 week double blind treatment period and washout. Adverse events (AEs) occurring following start of treatment or increasing in severity were counted as treatment emergent. Population analysis was defined as all subjects who received any treatment during double blind period.

End point type	Other pre-specified

End point timeframe:

Week 4 (Visit 2) to Week 18 (Visit 6)

End point values	PF-05212377 30 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	91	94		
Units: Percentage of Subjects				
number (not applicable)	46.2	44.7		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Proportion of Laboratory Abnormalities of Potential Clinical Concern During Double Blind Period

End point title	Proportion of Laboratory Abnormalities of Potential Clinical Concern During Double Blind Period

End point description:

Proportion of subjects with lab abnormalities of potential clinical concern over the double blind period. The following parameters were analyzed: hematology (hemoglobin, hematocrit, red blood cell count, platelet count, white blood cell count, neutrophils, eosinophils, monocytes, basophils, lymphocytes); blood chemistry (blood urea nitrogen, creatinine, glucose, calcium, sodium, potassium, chloride, total bicarbonate, aspartate aminotransferase, alanine aminotransferase, bilirubin, alkaline phosphatase, uric

acid, albumin, and total protein; urinalysis (pH, glucose, protein/albumin, hemoglobin/blood, ketones/acetone, nitrites, leukocyte esterase, microscopy [if urine dipstick was positive for blood, protein, nitrites or leukocyte esterase]); others (only at screening or needed: urine drug screen, thyroid panel, VB12, methylmalonic acid, folate and HbA1). Analysis population was defined as all subjects who received any treatment during Week 4 (Visit 2) to Week 16 (Visit 5).

End point type	Other pre-specified

End point timeframe:

Week 4 (Visit 2) to Week 16 (Visit 5)

End point values	PF-05212377 30 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	91	94		
Units: Percentage of Subjects				
number (not applicable)	36	52		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Selected Electrocardiogram (ECG) Change from Baseline - PR Interval at Week 6 (Visit 3)

End point title	Selected Electrocardiogram (ECG) Change from Baseline - PR Interval at Week 6 (Visit 3)

End point description:

The PR interval is the time from the onset of the P wave to the start of the QRS complex (the combination of the Q wave, R wave and S wave, representing ventricular depolarization). The analysis population was defined as all subjects who received any treatment during Week 4 (Visit 2) to Week 16 (Visit 5).

End point type	Other pre-specified

End point timeframe:

Baseline and Week 6 (Visit 3)

End point values	PF-05212377 30 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	85	89		
Units: milliseconds (msec)				
arithmetic mean (full range (min-max))	-2.8 (-52 to 24)	-3.6 (-82 to 35)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Selected ECG Change from Baseline - PR Interval at Week 10 (Visit 4)

End point title	Selected ECG Change from Baseline - PR Interval at Week 10 (Visit 4)

End point description:

The PR interval is the time from the onset of the P wave to the start of the QRS complex (the combination of the Q wave, R wave and S wave, representing ventricular depolarization). The analysis population was defined as all subjects who received any treatment during Week 4 (Visit 2) to Week 16 (Visit 5).

End point type	Other pre-specified

End point timeframe:

Baseline and Week 10 (Visit 4)

End point values	PF-05212377 30 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	79	87		
Units: msec				
arithmetic mean (full range (min-max))	-0.1 (-42 to 23)	-1.3 (-61 to 61)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Selected ECG Change from Baseline - PR Interval at Week 16/Early Termination (Visit 5)

End point title	Selected ECG Change from Baseline - PR Interval at Week 16/Early Termination (Visit 5)

End point description:

The PR interval is the time from the onset of the P wave to the start of the QRS complex (the combination of the Q wave, R wave and S wave, representing ventricular depolarization). The analysis population was defined as all subjects who received any treatment during Week 4 (Visit 2) to Week 16 (Visit 5).

End point type	Other pre-specified

End point timeframe:

Baseline and Week 16/Early Termination (Visit 5)

End point values	PF-05212377 30 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	82	85		
Units: msec				
arithmetic mean (full range (min-max))	-2.5 (-69 to 24)	-1.6 (-49 to 33)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Proportion of PR Interval Abnormalities of Potential Clinical Concern

End point title	Proportion of PR Interval Abnormalities of Potential Clinical Concern

End point description:

Proportion (%) of subjects with PR Interval abnormalities meeting categorical criteria over the 12 week double blind treatment period. The PR interval is the time from the onset of the P wave to the start of the QRS complex (the combination of the Q wave, R wave and S wave, representing ventricular depolarization). Subjects with post-baseline PR absolute value>=300 msec , a PR increase of >=25% (for subjects with a baseline value>=200 msec), or with an increase >=50% (for subjects with a baseline value<200 msec) were counted. The analysis population was defined as all subjects who received any treatment during Week 4 (Visit 2) to Week 16 (Visit 5).

End point type	Other pre-specified

End point timeframe:

Week 4 (Visit 2) to Week 16 (Visit 5)

End point values	PF-05212377 30 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	86	90		
Units: Percentage of Subjects				
number (not applicable)				
Post-Baseline Maximum Absolute Value >=300 msec	0	4.4		
Post-Baseline Maximum Increase >=25/50%	0	0		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Selected ECG Change from Baseline - QRS complex at Week 6 (Visit 3)

End point title	Selected ECG Change from Baseline - QRS complex at Week 6 (Visit 3)

End point description:

The QRS complex is the combination of the Q wave, R wave and S wave, representing ventricular depolarization.The analysis population was defined as all subjects who received any treatment during Week 4 (Visit 2) to Week 16 (Visit 5).

End point type	Other pre-specified

End point timeframe:

Baseline and Week 6 (Visit 3)

End point values	PF-05212377 30 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	88	92		
Units: msec				
arithmetic mean (full range (min-max))	-0.3 (-22 to 43)	-0.8 (-14 to 10)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Selected ECG Change from Baseline - QRS complex at Week 10 (Visit 4)

End point title	Selected ECG Change from Baseline - QRS complex at Week 10 (Visit 4)

End point description:

The QRS complex is the combination of the Q wave, R wave and S wave, representing ventricular depolarization). The analysis population was defined as all subjects who received any treatment during Week 4 (Visit 2) to Week 16 (Visit 5).

End point type	Other pre-specified

End point timeframe:

Baseline and Week 10 (Visit 4)

End point values	PF-05212377 30 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	81	90		
Units: msec				
arithmetic mean (full range (min-max))	-0.1 (-13 to 45)	0.1 (-15 to 22)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Selected ECG Change from Baseline - QRS complex at Week 16/Early Termination (Visit 5)

End point title	Selected ECG Change from Baseline - QRS complex at Week 16/Early Termination (Visit 5)

End point description:

The QRS complex is the combination of the Q wave, R wave and S wave, representing ventricular depolarization. The analysis population was defined as all subjects who received any treatment during Week 4 (Visit 2) to Week 16 (Visit 5).

End point type	Other pre-specified

End point timeframe:

Baseline and Week 16/Early Termination (Visit 5)

End point values	PF-05212377 30 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	85	89		
Units: msec				
arithmetic mean (full range (min-max))	0.1 (-14 to 18)	-0.3 (-21 to 14)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Proportion of Subjects with QRS Complex Abnormalities of Potential Clinical Concern

End point title	Proportion of Subjects with QRS Complex Abnormalities of Potential Clinical Concern

End point description:

Proportion (%) of subjects with QRS complex abnormalities meeting categorical criteria over the 12 week double blind treatment period. The QRS complex is the combination of the Q wave, R wave and S wave, representing ventricular depolarization). Subjects with post-baseline QRS complex absolute value>=100 msec , a QRS complex increase of >=25% (for subjects with a baseline value>=100 msec), or with an increase >=50% (for subjects with a baseline value<100 msec) were counted. The analysis population was defined as all subjects who received any treatment during Week 4 (Visit 2) to Week 16 (Visit 5).

End point type	Other pre-specified

End point timeframe:

Week 4 (Visit 2) to Week 16 (Visit 5)

End point values	PF-05212377 30 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	91	93		
Units: Percentage of Subjects				
number (not applicable)				
Post-Baseline Maximum Absolute Value >=200 msec	0	0		
Post-Baseline Maximum Increase >=25/50%	0	0		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Selected ECG Change from Baseline - QTcF interval at Week 6 (Visit 3)

End point title	Selected ECG Change from Baseline - QTcF interval at Week 6 (Visit 3)

End point description:

The QTcF interval is a measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle, which is corrected for heart rate using Fridericia's formula. The analysis population was defined as all subjects who received any treatment during Week 4 (Visit 2) to Week 16 (Visit 5).

End point type	Other pre-specified

End point timeframe:

Baseline and Week 6 (Visit 3)

End point values	PF-05212377 30 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	88	92		
Units: msec				
arithmetic mean (full range (min-max))	-3 (-31 to 37)	-4.9 (-35 to 35)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Selected ECG Change from Baseline - QTcF interval at Week 10 (Visit 4)

End point title	Selected ECG Change from Baseline - QTcF interval at Week 10 (Visit 4)

End point description:

The QTcF interval is a measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle, which is corrected for heart rate using Fridericia's formula. The analysis population was defined as all subjects who received any treatment during Week 4 (Visit 2) to Week 16 (Visit 5).

End point type	Other pre-specified

End point timeframe:

Baseline and Week 10 (Visit 4)

End point values	PF-05212377 30 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	81	90		
Units: msec				
arithmetic mean (full range (min-max))	-0.2 (-38 to 47)	-5.5 (-40 to 48)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Selected ECG Change from Baseline - QTcF interval at Week 16/Early Termination (Visit 5)

End point title	Selected ECG Change from Baseline - QTcF interval at Week 16/Early Termination (Visit 5)

End point description:

The QTcF interval is a measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle, which is corrected for heart rate using Fridericia's formula. The analysis population was defined as all subjects who received any treatment during Week 4 (Visit 2) to Week 16 (Visit 5).

End point type	Other pre-specified

End point timeframe:

Baseline and Week 16/Early Termination (Visit 5)

End point values	PF-05212377 30 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	85	89		
Units: msec				
arithmetic mean (full range (min-max))	0.8 (-31 to 34)	-2.2 (-62 to 30)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Proportion of Subjects with QTcF Interval Abnormalities of Potential Clinical Concern

End point title	Proportion of Subjects with QTcF Interval Abnormalities of Potential Clinical Concern

End point description:

Proportion (%) of subjects with QTcF Interval abnormalities meeting categorical criteria over the 12-

week double blind treatment period. The QTcF interval is a measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle, which is corrected for heart rate using Fridericia's formula. Subjects with a post-baseline QTcF absolute value of 450 - <480, 480 - <500, or >=500 mec, or with a post-baseline QTcF increase of 30 - <60 or >=60 msec were counted. The analysis population was defined as all subjects who received any treatment during Week 4 (Visit 2) to Week 16 (Visit 5).

End point type	Other pre-specified

End point timeframe:

Week 4 (Visit 2) to Week 16 (Visit 5)

End point values	PF-05212377 30 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	91	93		
Units: Percentage of Subjects				
number (not applicable)				
Post-Baseline Absolute Value of 450-<480 msec	15.4	14		
Post-Baseline Absolute Value of 480-<500 msec	4.4	1.1		
Change from Baseline of 30 -<60 msec	6.6	3.2		
Change from Baseline >=60 msec	0	0		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Blood Pressure (BP) Changes from Baseline - Week 6 (Visit 3)

End point title	Blood Pressure (BP) Changes from Baseline - Week 6 (Visit 3)

End point description:

The BP changes from baseline at Week 6 (Visit 3) including supine systolic BP, standing systolic BP, standing systolic BP, supine diastolic BP, standing diastolic BP.The analysis population was defined as all subjects who received any treatment during Week 4 (Visit 2) to Week 16 (Visit 5).

End point type	Other pre-specified

End point timeframe:

Baseline and Week 6 (Visit 3)

End point values	PF-05212377 30 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	89	93		
Units: millimeters of mercury (mm Hg)				
arithmetic mean (full range (min-max))				
Supine Systolic BP	-3.6 (-38 to 19)	-3.9 (-52 to 30)		
Standing Systolic BP	-4.1 (-49 to 20)	-3 (-38 to 22)		

Supine Diastolic BP	-2.2 (-37 to 26)	-1.8 (-33 to 20)		
Standing Diastolic BP	-1.1 (-23 to 17)	-1 (-23 to 21)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Pulse Rate Changes from Baseline - Week 6 (Visit 3)

End point title	Pulse Rate Changes from Baseline - Week 6 (Visit 3)

End point description:

The pulse rate changes from baseline at Week 6 (Visit 3) including supine pulse rate, and standing pulse rate. The analysis population was defined as all subjects who received any treatment during Week 4 (Visit 2) to Week 16 (Visit 5).

End point type	Other pre-specified

End point timeframe:

Baseline and Week 6 (Visit 3)

End point values	PF-05212377 30 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	89	93		
Units: beats per minute (bpm)				
arithmetic mean (full range (min-max))				
Supine Pulse Rate	-1.4 (-30 to 30)	1.4 (-21 to 20)		
Standing Pulse Rate	-0.3 (-20 to 30)	1.3 (-12 to 27)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: BP Changes from Baseline - Week 10 (Visit 4)

End point title	BP Changes from Baseline - Week 10 (Visit 4)

End point description:

The BP changes from baseline at Week 10 (Visit 4) including supine systolic BP, standing systolic BP, standing systolic BP, supine diastolic BP, standing diastolic BP. The analysis population was defined as all subjects who received any treatment during Week 4 (Visit 2) to Week 16 (Visit 5).

End point type	Other pre-specified

End point timeframe:

Baseline and Week 10 (Visit 4)

End point values	PF-05212377 30 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	81	91		
Units: mm Hg				
arithmetic mean (full range (min-max))				
Supine Systolic BP	-3.4 (-36 to 20)	-0.3 (-68 to 34)		
Standing Systolic BP	-3.8 (-33 to 32)	0.8 (-49 to 49)		
Supine Diastolic BP	-2.4 (-32 to 20)	-0.7 (-39 to 25)		
Standing Diastolic BP	-1.2 (-20 to 20)	0.3 (-26 to 39)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Pulse Rate Changes from Baseline - Week 10 (Visit 4)

End point title	Pulse Rate Changes from Baseline - Week 10 (Visit 4)

End point description:

The pulse rate changes from baseline at Week 10 (Visit 4) including supine pulse rate, and standing pulse rate. The analysis population was defined as all subjects who received any treatment during Week 4 (Visit 2) to Week 16 (Visit 5).

End point type	Other pre-specified

End point timeframe:

Baseline and Week 10 (Visit 4)

End point values	PF-05212377 30 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	81	91		
Units: bpm				
arithmetic mean (full range (min-max))				
Supine Pulse Rate	-0.4 (-26 to 22)	0.5 (-24 to 17)		
Standing Pulse Rate	-0.7 (-20 to 24)	1.8 (-19 to 21)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: BP Changes from Baseline - Week 16/Early Termination (Visit 5)

End point title	BP Changes from Baseline - Week 16/Early Termination (Visit

	5)

End point description:

The BP changes from baseline at Week 16/Early Termination (Visit 5) including supine systolic BP, standing systolic BP, standing systolic BP, supine diastolic BP, standing diastolic BP. The analysis population was defined as all subjects who received any treatment during Week 4 (Visit 2) to Week 16 (Visit 5).

End point type	Other pre-specified

End point timeframe:

Baseline and Week 16/Early Termination (Visit 5)

End point values	PF-05212377 30 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	85	90		
Units: mmHg				
arithmetic mean (full range (min-max))				
Supine Systolic BP	-1.4 (-30 to 27)	-1.1 (-30 to 72)		
Standing Systolic BP	-1 (-30 to 32)	-1.1 (-26 to 66)		
Supine Diastolic BP	-2.1 (-39 to 22)	-0.3 (-18 to 35)		
Standing Diastolic BP	-0.8 (-23 to 23)	0 (-20 to 36)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Pulse Rate Changes from Baseline - Week 16/Early Termination (Visit 5)

End point title	Pulse Rate Changes from Baseline - Week 16/Early Termination (Visit 5)

End point description:

The pulse rate changes from baseline at Week 16/Early Termination (Visit 5) including supine pulse rate, and standing pulse rate. The analysis population was defined as all subjects who received any treatment during Week 4 (Visit 2) to Week 16 (Visit 5).

End point type	Other pre-specified

End point timeframe:

Baseline and Week 16/Early Termination (Visit 5)

End point values	PF-05212377 30 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	85	90		
Units: bpm				
arithmetic mean (full range (min-max))				
Supine Pulse Rate	-0.8 (-29 to 31)	0.6 (-22 to 20)		
Standing Pulse Rate	-1.9 (-24 to 39)	0.8 (-17 to 17)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Proportion of Subjects with Post-Baseline Vital Signs Abnormalities of Potential Clinical Concern

End point title	Proportion of Subjects with Post-Baseline Vital Signs Abnormalities of Potential Clinical Concern

End point description:

Proportion (%) of subjects with vital signs abnormalities (absolute and change from baseline) meeting categorical criteria over the 12-week double blind treatment period were counted. Vital signs data included BP and pulse rate. The analysis population was defined as all subjects who received any treatment during Week 4 (Visit 2) to Week 16 (Visit 5).

End point type	Other pre-specified

End point timeframe:

Week 4 (Visit 2) to Week 16 (Visit 5)

End point values	PF-05212377 30 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	91	94		
Units: Percentage of Subjects				
number (not applicable)				
Absolute Supine Systolic BP<90 mmHg	0	1.1		
Absolute Standing Systolic BP<90 mmHg	0	1.1		
Absolute Supine Diastolic BP<50 mmHg	0	2.1		
Absolute Standing Diastolic BP <50 mmHg	0	0		
Absolute Supine Pulse Rate <40 bpm	0	0		
Absolute Supine Pulse Rate >120 bpm	0	0		
Absolute Standing Pulse Rate <40 bpm	0	0		
Absolute Standing Pulse Rate >140 bpm	0	0		
Increase in Supine Systolic BP>=30 mmHg	0	5.3		
Increase in Standing Systolic BP>=30 mmHg	2.2	3.2		
Increase in Supine Diastolic BP >=20 mmHg	4.4	4.3		

Increase in Standing Diastolic BP >=20 mmHg	3.3	5.3		
Decrease in Supine Systolic BP>=30 mmHg	5.5	5.3		
Decrease in Standing Systolic BP>=30 mmHg	5.5	5.3		
Decrease in Supine Diastolic BP >=20 mmHg	8.8	5.3		
Decrease in Standing Diastolic BP >=20 mmHg	4.4	6.4		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Subjects in Each Category of C-CASA Mapped from the C-SSRS Responses

End point title	Subjects in Each Category of C-CASA Mapped from the C-SSRS Responses

End point description:

Subjects in each category of the Columbia Classification Algorithm of Suicide Assessment (C-CASA) mapped from the Columbia-Suicide Severity Rating Scale (C-SSRS) responses were reported. C-CASA Event Code: <1> Completed suicide; <2> Suicide attempt; <3> Preparatory acts towards imminent suicidal behavior; <4> Suicidal Ideation; <7> Self-injurious behavior, no suicidal intent. The suicidality assessments were performed at Screening, Week 0 (Visit 1), Week 4 (Visit 2), Week 6, (Visit 3), Week 10 (Visit 4), Week 16 (Visit 5), and Week 18 (Visit 6). Only subjects falling any category of C-CASA events were listed below. Analysis population was defined as all subjects screened and assigned.

End point type	Other pre-specified

End point timeframe:

From Screening to Week 18/Early Termination (Visit 6)

End point values	PF-05212377 30 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	91	94		
Units: subjects				
number (not applicable)				
Week 4 (Visit 2): <4>	2	1		
Week 6 (Visit 3): <4>	0	1		
Week 10 (Visit 4): <4>	2	0		
Week 16/Early Termination (Visit 5): <4>	1	0		
Week 6 (Visit 3): <7>	1	0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Baseline up to Week 18	
Assessment type	Non-systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	18.1
Reporting groups	
Reporting group title	Placebo Run-in
Reporting group description: Subjects who received placebo during the single blind placebo-run in period	
Reporting group title	Placebo
Reporting group description: Subjects who received placebo once daily in the morning during the double blind period.	
Reporting group title	PF-05212377 30 mg
Reporting group description: Subjects who received PF-05212377 30 mg once daily in the morning during the double blind period.	

Serious adverse events	Placebo Run-in	Placebo	PF-05212377 30 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 195 (0.51%)	3 / 94 (3.19%)	5 / 91 (5.49%)
number of deaths (all causes)	0	0	1
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Femoral neck fracture			
subjects affected / exposed	1 / 195 (0.51%)	0 / 94 (0.00%)	0 / 91 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Foreign body			
subjects affected / exposed	0 / 195 (0.00%)	1 / 94 (1.06%)	0 / 91 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Orthostatic hypotension			
subjects affected / exposed	0 / 195 (0.00%)	0 / 94 (0.00%)	1 / 91 (1.10%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Cardiac disorders			
Bradycardia			
subjects affected / exposed	0 / 195 (0.00%)	0 / 94 (0.00%)	2 / 91 (2.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Accidental death			
subjects affected / exposed	0 / 195 (0.00%)	0 / 94 (0.00%)	1 / 91 (1.10%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Asthenia			
subjects affected / exposed	0 / 195 (0.00%)	0 / 94 (0.00%)	1 / 91 (1.10%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	0 / 195 (0.00%)	0 / 94 (0.00%)	1 / 91 (1.10%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Delirium			
subjects affected / exposed	0 / 195 (0.00%)	1 / 94 (1.06%)	0 / 91 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Pneumonia			
subjects affected / exposed	0 / 195 (0.00%)	1 / 94 (1.06%)	0 / 91 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 195 (0.00%)	0 / 94 (0.00%)	1 / 91 (1.10%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 2 %

Non-serious adverse events	Placebo Run-in	Placebo	PF-05212377 30 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	13 / 195 (6.67%)	20 / 94 (21.28%)	25 / 91 (27.47%)
Investigations			
Weight decreased			
subjects affected / exposed	1 / 195 (0.51%)	2 / 94 (2.13%)	0 / 91 (0.00%)
occurrences (all)	1	2	0
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	2 / 195 (1.03%)	3 / 94 (3.19%)	3 / 91 (3.30%)
occurrences (all)	2	3	3
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 195 (0.00%)	1 / 94 (1.06%)	2 / 91 (2.20%)
occurrences (all)	0	1	2
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 195 (0.00%)	2 / 94 (2.13%)	2 / 91 (2.20%)
occurrences (all)	0	2	2
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	6 / 195 (3.08%)	3 / 94 (3.19%)	8 / 91 (8.79%)
occurrences (all)	6	3	9
Psychiatric disorders			
Hallucination			
subjects affected / exposed	0 / 195 (0.00%)	2 / 94 (2.13%)	0 / 91 (0.00%)
occurrences (all)	0	2	0
Insomnia			
subjects affected / exposed	0 / 195 (0.00%)	2 / 94 (2.13%)	1 / 91 (1.10%)
occurrences (all)	0	3	1
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 195 (0.00%)	1 / 94 (1.06%)	2 / 91 (2.20%)
occurrences (all)	0	1	2
Nasopharyngitis			

subjects affected / exposed	4 / 195 (2.05%)	2 / 94 (2.13%)	2 / 91 (2.20%)
occurrences (all)	4	2	2
Pneumonia			
subjects affected / exposed	0 / 195 (0.00%)	2 / 94 (2.13%)	0 / 91 (0.00%)
occurrences (all)	0	2	0
Upper respiratory tract infection			
subjects affected / exposed	0 / 195 (0.00%)	1 / 94 (1.06%)	2 / 91 (2.20%)
occurrences (all)	0	1	2
Urinary tract infection			
subjects affected / exposed	0 / 195 (0.00%)	4 / 94 (4.26%)	5 / 91 (5.49%)
occurrences (all)	0	4	5

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 June 2013	The inclusion and exclusion criteria were amended and some more efficacy evaluations were added
02 January 2014	Numbering of Days for Screening Period was revised. Some sections were reworded

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported