Clinical trial results:
A Phase 2, Randomized, Double-Blind, Placebo-Controlled, Parallel Group, Multi-Center Study to Evaluate the Efficacy and Safety of Once-Daily Administration of a Chemokine CCR2/5 Receptor Antagonist (PF-04634817) in Adults With Type 2 Diabetes and Overt Nephropathy

Due to the EudraCT – Results system being out of service between 31 July 2015 and 12 January 2016, these results have been published in compliance with revised timelines.

Summary

EudraCT number	2012-003332-23
Trial protocol	IT DE ES PL RO
Global end of trial date	22 September 2014

Results information

Result version number	v1 (current)
This version publication date	29 July 2016
First version publication date	29 July 2016

Trial information

Trial identification

Sponsor protocol code	B1261007

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01712061
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 ClinicalTrials.gov Call Center, 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	01 September 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	22 September 2014
Global end of trial reached?	Yes
Global end of trial date	22 September 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of the trial was to evaluate the efficacy of PF-04634817 compared to placebo in the reduction of albuminuria following 12 weeks of treatment in subjects with Type 2 diabetes and overt nephropathy.

Protection of trial subjects:

This study used an unblinded Internal Review Committee (IRC) for the interim analysis.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	13 December 2012
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	Argentina: 6
Country: Number of subjects enrolled	Australia: 14
Country: Number of subjects enrolled	Germany: 12
Country: Number of subjects enrolled	Hong Kong: 3
Country: Number of subjects enrolled	Italy: 8
Country: Number of subjects enrolled	Canada: 23
Country: Number of subjects enrolled	Korea, Republic of: 9
Country: Number of subjects enrolled	Malaysia: 5
Country: Number of subjects enrolled	Peru: 10
Country: Number of subjects enrolled	Poland: 8
Country: Number of subjects enrolled	Romania: 11
Country: Number of subjects enrolled	United States: 107
Country: Number of subjects enrolled	Spain: 10
Worldwide total number of subjects	226
EEA total number of subjects	49

Notes:

Subjects enrolled per age group

In utero	0

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)	112
From 65 to 84 years	114
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

The primary entry criterion for participants was based on presence of macroalbuminuria (urine albumin to creatinine ratio [UACR] greater than or equal to (>=)300 milligrams per gram (mg/g).

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

Arms

Are arms mutually exclusive?	No
Arm title	PF-04634817 150 mg Daily

Arm description:

Subjects with estimated glomerular filtration rate (eGFR) values of 20 to less than (<)30 milliliters/minute (mL/min)/1.73 square meter (m^2) were dosed orally at 150 mg once daily for 12 weeks.

Arm type	Experimental
Investigational medicinal product name	PF-04634817
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

150 mg

Arm title	PF-04634817 200 mg Daily

Arm description:

Subjects with eGFR values of 30 to 75 mL/min/1.73 m^2 were dosed orally at 200 mg once daily for 12 weeks.

Arm type	Experimental
Investigational medicinal product name	PF-04634817
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

200 mg

Arm title	PF-04634817 200 mg/150 mg Daily

Arm description:

Subjects received either 150 mg or 200 mg once daily for 12 weeks.

Arm type	Experimental

Investigational medicinal product name	PF-04634817
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

150 mg or 200 mg once daily

Arm title	Placebo Daily

Arm description:

Subjects were dosed orally with matching placebo tablets once daily for 12 weeks.

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

Dosage and administration details:

placebo matched PF-04634817

Number of subjects in period 1	PF-04634817 150 mg Daily	PF-04634817 200 mg Daily	PF-04634817 200 mg/150 mg Daily
Started	30	140	170
Completed	20	114	134
Not completed	10	26	36
Adverse event, serious fatal	-	-	-
Consent withdrawn by subject	1	7	8
Did Not Meet Entrance Criteria	4	6	10
Adverse event, non-fatal	4	9	13
Medication Error Without Associated AE	-	1	1
Unspecified	-	3	3
Lost to follow-up	1	-	1

Number of subjects in period 1	Placebo Daily
Started	56
Completed	45
Not completed	11
Adverse event, serious fatal	1
Consent withdrawn by subject	1
Did Not Meet Entrance Criteria	3
Adverse event, non-fatal	5
Medication Error Without Associated AE	-
Unspecified	-
Lost to follow-up	1

Baseline characteristics

Reporting groups	
Reporting group title	Overall Study

Reporting group description: -

Reporting group values	Overall Study	Total	
Number of subjects	226	226	
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)	112	112	
From 65-84 years	114	114	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	64.1		
standard deviation	± 8.6	-	
Gender, Male/Female Units: Participants			
FEMALE	43	43	
MALE	183	183	

End points

End points reporting groups

Reporting group title	PF-04634817 150 mg Daily
Reporting group description:	
Subjects with estimated glomerular filtration rate (eGFR) values of 20 to less than (<)30 milliliters/minute (mL/min)/1.73 square meter (m^2) were dosed orally at 150 mg once daily for 12 weeks.	
Reporting group title	PF-04634817 200 mg Daily
Reporting group description:	
Subjects with eGFR values of 30 to 75 mL/min/1.73 m^2 were dosed orally at 200 mg once daily for 12 weeks.	
Reporting group title	PF-04634817 200 mg/150 mg Daily
Reporting group description:	
Subjects received either 150 mg or 200 mg once daily for 12 weeks.	
Reporting group title	Placebo Daily
Reporting group description:	
Subjects were dosed orally with matching placebo tablets once daily for 12 weeks.	

Primary: Percent Reduction From Baseline in Urinary Albumin to Creatinine Ratio (UACR) at Week 12

End point title	Percent Reduction From Baseline in Urinary Albumin to Creatinine Ratio (UACR) at Week 12[1]
End point description:	
End point type	Primary
End point timeframe:	
Baseline and Week 12	

Notes:

[1] - 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: No statistical analysis was planned for this safety endpoint. Safety data were summarized using Sponsor Data Standards.

End point values	PF-04634817 200 mg/150 mg Daily	Placebo Daily		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	159	51		
Units: percent (%)				
arithmetic mean (confidence interval 95%)	13.27 (3.14 to 24.62)	5.02 (-7.9 to 18.7)		

Statistical analyses

Statistical analysis title	Percent Reduction from Baseline in UACR at Week 12
Comparison groups	PF-04634817 200 mg/150 mg Daily v Placebo Daily

Number of subjects included in analysis	210
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Bayesian ANCOVA
Point estimate	0.91785
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.75
upper limit	1.09

Secondary: Change From Baseline in UACR at Weeks 4, 8 and 16

End point title	Change From Baseline in UACR at Weeks 4, 8 and 16[2]

End point description:

The presence of albumin in the urine (macroalbuminuria) is a marker of kidney disease. Albumin and creatinine concentrations were obtained from spot urine samples.

End point type	Secondary

End point timeframe:

Baseline, Weeks 4, 8 and 16

Notes:

[2] - 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: No statistical analysis was planned for this secondary endpoint. Secondary analyses included tabulations of summary statistics of all continuous secondary endpoints.

End point values	PF-04634817 200 mg/150 mg Daily	Placebo Daily		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	159	51		
Units: mg/millimolar creatinine (mmolCr)				
geometric mean (geometric coefficient of variation)				
Baseline (n=157,50)	127.41 (± 96)	121.8 (± 88)		
Change From Baseline at Week 4 (n=148,46)	0.89 (± 66)	0.91 (± 88)		
Change From Baseline at Week 8 (n=134,43)	0.9 (± 62)	0.94 (± 57)		
Change From Baseline at Week 16 (n=126,37)	0.93 (± 72)	0.92 (± 56)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Urinary Protein to Creatinine Ratio (UPCR) at Weeks 4, 8, 12 and 16

End point title	Change From Baseline in Urinary Protein to Creatinine Ratio (UPCR) at Weeks 4, 8, 12 and 16[3]

End point description:

The presence of protein in the urine (proteinuria) often implies kidney disease. Protein and creatinine concentrations were obtained from spot urine samples.

End point type	Secondary

End point timeframe:

Baseline, Weeks 4, 8, 12 and 16

Notes:

[3] - 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: No statistical analysis was planned for this secondary endpoint. Secondary analyses included tabulations of summary statistics of all continuous secondary endpoints.

End point values	PF-04634817 200 mg/150 mg Daily	Placebo Daily		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	159	51		
Units: mg/mmolCr				
geometric mean (geometric coefficient of variation)				
Baseline (n=155,49)	185.42 (± 97)	176.31 (± 82)		
Change From Baseline at Week 4 (n=143,45)	0.93 (± 47)	0.92 (± 76)		
Change From Baseline at Week 8 (n=130,42)	0.92 (± 50)	0.94 (± 46)		
Change From Baseline at Week 12 (n=125,42)	0.92 (± 58)	0.92 (± 79)		
Change From Baseline at Week 16 (n=125,36)	0.95 (± 58)	0.92 (± 55)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Estimated Glomerular Filtration Rate (eGFR) Using the Abbreviated Modified Diet in Renal Disease (MDRD) Formula at Weeks 1, 4, 8, 12 and 16

End point title	Change From Baseline in Estimated Glomerular Filtration Rate (eGFR) Using the Abbreviated Modified Diet in Renal Disease (MDRD) Formula at Weeks 1, 4, 8, 12 and 16[4]

End point description:

eGFR was calculated using the MDRD equation and normalized to 1.73 m^2 body surface area. Age and corresponding creatinine at each visit (Weeks 1, 4, 8, 12 and 16) were used to calculate GFR

End point type	Secondary

End point timeframe:

Baseline, Week 1, 4, 8, 12 and 16

Notes:

[4] - 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: The warning is not true, statistical analysis was reported for all the arms in the baseline period.

End point values	PF-04634817 200 mg/150 mg Daily	Placebo Daily		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	159	51		
Units: mL/min/1.73m^2				
arithmetic mean (standard deviation)				
Baseline (n=159,51)	41.8 (± 12.18)	41.65 (± 13.46)		
Change From Baseline at Week 1 (n=157,50)	-0.77 (± 5.8)	-0.35 (± 5.28)		
Change From Baseline at Week 4 (n=157,51)	-1.07 (± 5.37)	-1.32 (± 5.12)		
Change From Baseline at Week 8 (n=147,47)	-1.6 (± 5.34)	-2.15 (± 6.83)		
Change From Baseline at Week 12 (n=136,45)	-1.14 (± 5.7)	-1.03 (± 5.75)		
Change From Baseline at Week 16 (n=134,44)	-2.14 (± 6.42)	-1.18 (± 5.58)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in eGFR Using Cystatin Formula at Weeks 12 and 16

End point title	Change From Baseline in eGFR Using Cystatin Formula at Weeks 12 and 16[5]

End point description:

Serum cystatin C may be a more reliable endogenous marker of GFR than serum creatinine. eGFR was calculated using the Cystatin Formula and normalized to 1.73 m^2 body surface area.

End point type	Secondary

End point timeframe:

Baseline, Week 12, and Week 16

Notes:

[5] - 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: No statistical analysis was planned for this secondary endpoint. Secondary analyses included tabulations of summary statistics of all continuous secondary endpoints.

End point values	PF-04634817 200 mg/150 mg Daily	Placebo Daily		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	159	51		
Units: mL/min/1.73m^2				
arithmetic mean (standard deviation)				
Baseline (n=159,50)	45.28 (± 14.22)	45.36 (± 14.94)		
Change From Baseline at Week 12 (n=135,44)	-1.1 (± 6.3)	-0.7 (± 5.49)		
Change From Baseline at Week 16 (n=134,43)	-2.27 (± 6.77)	-0.91 (± 6.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Serum Creatinine at Weeks 1, 4, 8, 12 and 16

End point title	Change From Baseline in Serum Creatinine at Weeks 1, 4, 8, 12 and 16[6]

End point description:

Serum creatinine is an indicator of kidney function. Creatinine is a substance formed from the metabolism of creatine, commonly found in blood, urine, and muscle tissue. It is removed from the blood by the kidneys and excreted in urine. Normal adult blood levels of creatinine=45 to 90 micromoles per liter (mcmol/L) for females, 60 to 110 mcmol/L for males, however normal values are age-dependent. Change from baseline=creatinine level at Week 1, 4, 8, 12 or 16 minus baseline level where higher scores represented decreased kidney function.

End point type	Secondary

End point timeframe:

Baseline, Week 1, 4, 8, 12 and 16

Notes:

[6] - 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: No statistical analysis was planned for this secondary endpoint. Secondary analyses included tabulations of summary statistics of all continuous secondary endpoints.

End point values	PF-04634817 200 mg/150 mg Daily	Placebo Daily		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	159	51		
Units: milligrams per deciliter (mg/dL)				
arithmetic mean (standard deviation)				
Baseline (n=159,51)	1.72 (± 0.51)	1.77 (± 0.51)		
Change From Baseline at Week 1 (n=158,50)	0.05 (± 0.22)	0.03 (± 0.17)		
Change From Baseline at Week 4 (n=157,51)	0.06 (± 0.21)	0.11 (± 0.3)		
Change From Baseline at Week 8 (n=147,47)	0.06 (± 0.21)	0.09 (± 0.24)		
Change From Baseline at Week 12 (n=137,45)	0.05 (± 0.24)	0.08 (± 0.2)		
Change From Baseline at Week 16 (n=134,44)	0.09 (± 0.3)	0.09 (± 0.29)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Serum Cystatin C at Weeks 12 and 16

End point title	Change From Baseline in Serum Cystatin C at Weeks 12 and

End point description:

Cystatin C is a protein which is mainly used as a biomarker of kidney function. If kidney function and GFR decline, the blood levels of cystatin C rise.

End point type	Secondary

End point timeframe:

Baseline, Week 12, and Week 16

Notes:

[7] - 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: No statistical analysis was planned for this secondary endpoint. Secondary analyses included tabulations of summary statistics of all continuous secondary endpoints.

End point values	PF-04634817 200 mg/150 mg Daily	Placebo Daily		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	159	51		
Units: mg/dL				
arithmetic mean (standard deviation)				
Baseline (n=159,51)	1.54 (± 0.43)	1.52 (± 0.41)		
Change From Baseline at Week 12 (n=136,45)	0.03 (± 0.25)	0.03 (± 0.21)		
Change From Baseline at Week 16 (n=134,44)	0.05 (± 0.26)	0.06 (± 0.25)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Plasma Glycosylated Hemoglobin (HbA1c) at Weeks 4, 8, 12 and 16

End point title	Change From Baseline in Plasma Glycosylated Hemoglobin (HbA1c) at Weeks 4, 8, 12 and 16[8]

End point description:

HbA1c is a form of hemoglobin that is measured primarily to identify the average plasma glucose concentration over prolonged periods of time. As the average amount of plasma glucose increases, the fraction of HbA1c increases in a predictable way.

End point type	Secondary

End point timeframe:

Baseline, Weeks 4, 8, 12 and 16

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: No statistical analysis was planned for this secondary endpoint. Secondary analyses included tabulations of summary statistics of all continuous secondary endpoints.

End point values	PF-04634817 200 mg/150 mg Daily	Placebo Daily		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	159	51		
Units: percent				
arithmetic mean (standard deviation)				
Baseline (n=159,51)	7.51 (± 1.22)	7.91 (± 1.42)		
Change From Baseline at Week 4 (n=157,51)	0.03 (± 0.46)	-0.04 (± 0.46)		
Change From Baseline at Week 8 (n=147,46)	-0.02 (± 0.64)	-0.08 (± 0.71)		
Change From Baseline at Week 12 (n=137,44)	-0.01 (± 0.76)	-0.06 (± 0.81)		
Change From Baseline at Week 16 (n=133,44)	0.04 (± 0.89)	-0.04 (± 1.13)		

Statistical analyses

No statistical analyses for this end point

Secondary: Summary of Plasma PF-04634817 Pharmacokinetic (PK) Concentrations at Day 1 and Weeks 1, 4, 8 and 12

End point title	Summary of Plasma PF-04634817 Pharmacokinetic (PK) Concentrations at Day 1 and Weeks 1, 4, 8 and 12[9]

End point description:

End point type	Secondary

End point timeframe:

1, 2, 4 hours post-dose on Day 1; 2 hours post-dose on Weeks 1, 4, 8 and 12

Notes:

[9] - 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: No statistical analysis was planned for this secondary endpoint. Secondary analyses included tabulations of summary statistics of all continuous secondary endpoints.

End point values	PF-04634817 150 mg Daily	PF-04634817 200 mg Daily		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	30	140		
Units: ng/mL				
geometric mean (geometric coefficient of variation)				
Day 1: 1 Hour Post-Dose (n=29,124)	434.5 (± 65)	524.4 (± 83)		
Day 1: 2 Hours Post-Dose (n=30,139)	579.3 (± 37)	602.9 (± 52)		
Day 1: 4 Hours Post-Dose (n=29,137)	497.4 (± 38)	547.7 (± 46)		
Week 1: Pre-Dose (n=28,131)	294.4 (± 60)	231.2 (± 73)		
Week 1: 2 Hours Post-Dose (n=28,132)	884.8 (± 42)	865 (± 55)		
Week 4: Pre-Dose (n=25,126)	231.3 (± 51)	239.5 (± 87)		
Week 4: 2 Hours Post-Dose (n=24,122)	785.8 (± 45)	918 (± 55)		
Week 8: Pre-Dose (n=23,113)	310.2 (± 79)	245.2 (± 77)		
Week 8: 2 Hours Post-Dose (n=23,114)	730 (± 70)	895 (± 57)		
Week 12 (n=20,113)	320.1 (± 75)	252.3 (± 84)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change From Baseline in Systolic Blood Pressure (SBP) and Diastolic Blood Pressure (DBP) at Weeks 1, 4, 8, 12 and 16

End point title	Change From Baseline in Systolic Blood Pressure (SBP) and Diastolic Blood Pressure (DBP) at Weeks 1, 4, 8, 12 and 16[10]
End point description: Wk=Week	
End point type	Other pre-specified
End point timeframe: Baseline, Weeks 1, 4, 8, 12 and 16	

Notes:

[10] - 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: No statistical analysis was planned for this safety endpoint. Safety data were summarized using Sponsor Data Standards.

End point values	PF-04634817 200 mg/150 mg Daily	Placebo Daily		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	170	56		
Units: millimeters of mercury (mm Hg)				
arithmetic mean (standard deviation)				
Supine SBP: Baseline (n=168,53)	140.4 (± 13.96)	139.9 (± 13.6)		
Supine SBP:Change From Baseline Wk 1 (n=164,53)	-0.8 (± 12.75)	-1.6 (± 12.87)		
Supine SBP:Change From Baseline Wk 4 (n=154,49)	-0.5 (± 15.43)	-1.6 (± 14.19)		
Supine SBP:Change From Baseline Wk 8 (n=142,47)	-3.4 (± 12.94)	-1.1 (± 13.71)		
Supine SBP:Change From Baseline Wk 12 (n=134,45)	-2 (± 13.28)	-1.3 (± 13.23)		
Supine SBP:Change From Baseline Wk 16 (n=138,45)	-2.4 (± 15.14)	-0.3 (± 14.41)		
Supine DBP: Baseline (n=168,53)	75.9 (± 8.97)	77.1 (± 6.88)		
Supine DBP:Change From Baseline Wk 1 (n=164,53)	-0.2 (± 6.94)	-2.7 (± 7.58)		
Supine DBP:Change From Baseline Wk 4 (n=154,49)	0.1 (± 8.23)	-1.8 (± 7.47)		
Supine DBP:Change From Baseline Wk 8 (n=142,47)	-1.9 (± 7.46)	-1.5 (± 7.05)		
Supine DBP:Change From Baseline Wk 12 (n=134,45)	-0.9 (± 6.88)	-0.2 (± 6.69)		
Supine DBP:Change From Baseline Wk 16 (n=138,45)	-1.7 (± 7.98)	0.9 (± 8.4)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change From Baseline in Pulse Rate at Weeks 1, 4, 8, 12 and 16

End point title	Change From Baseline in Pulse Rate at Weeks 1, 4, 8, 12 and 16[11]

End point description:

End point type	Other pre-specified

End point timeframe:

Baseline, Weeks 1, 4, 8, 12 and 16

Notes:

[11] - 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: No statistical analysis was planned for this safety endpoint. Safety data were summarized using Sponsor Data Standards.

End point values	PF-04634817 200 mg/150 mg Daily	Placebo Daily		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	170	56		
Units: beats per minute (bpm)				
arithmetic mean (standard deviation)				
Baseline (n=168,53)	68.7 (± 9.74)	69.3 (± 9.3)		
Change From Baseline at Week 1 (n=164,53)	0.1 (± 5.86)	-0.7 (± 5.63)		
Change From Baseline at Week 4 (n=154,49)	0.3 (± 6.01)	-1 (± 6.63)		
Change From Baseline at Week 8 (n=142,47)	0.2 (± 6.54)	1.4 (± 6.77)		
Change From Baseline at Week 12 (n=134,45)	0.2 (± 7.03)	0.5 (± 7.33)		
Change From Baseline at Week 16 (n=138,45)	1.4 (± 8.22)	-0.1 (± 6.92)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change From Baseline in Body Weight at Weeks 1, 4, 8, 12 and 16

End point title	Change From Baseline in Body Weight at Weeks 1, 4, 8, 12 and 16[12]

End point description:

End point type	Other pre-specified

End point timeframe:

Baseline, Weeks 1, 4, 8, 12 and 16

Notes:

[12] - 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: No statistical analysis was planned for this safety endpoint. Safety data were summarized using Sponsor Data Standards.

End point values	PF-04634817 200 mg/150 mg Daily	Placebo Daily		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	170	56		
Units: kilograms (kg)				
arithmetic mean (standard deviation)				
Baseline (n=167,53)	93.8 (± 23.97)	95.1 (± 25.95)		
Change From Baseline at Week 1 (n=163,53)	0 (± 1.03)	0.3 (± 1.42)		
Change From Baseline at Week 4 (n=153,49)	0 (± 1.74)	0.4 (± 3.29)		
Change From Baseline at Week 8 (n=141,47)	0.1 (± 2.45)	0.7 (± 2.74)		
Change From Baseline at Week 12 (n=134,45)	0.3 (± 2.66)	0.7 (± 3.02)		
Change From Baseline at Week 16 (n=137,45)	-0.1 (± 2.79)	0.2 (± 3.37)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Number of Subjects With Laboratory Abnormalities Meeting the Criteria for Potential Clinical Concern

End point title	Number of Subjects With Laboratory Abnormalities Meeting the Criteria for Potential Clinical Concern[13]

End point description:

The following laboratory parameters were analyzed for abnormalities at any time point mentioned in the timeframe: clinical chemistry (sodium, potassium, chloride, bicarbonate, phosphate, glucose, blood urea nitrogen [BUN], creatinine, albumin, calcium, bilirubin [total, direct, and indirect], gamma-glutamyl transferase [GGT], alanine aminotransferase [ALT], aspartate aminotransferase [AST], lactic dehydrogenase [LDH], alkaline phosphatase, creatine phosphokinase [CPK], uric acid, amylase and lipase); hematology (hemoglobin, hematocrit, red blood cell [RBC] count, white blood cell [WBC] count with differential, and platelet count); FSH (for postmenopausal women who had been amenorrheic for less than 2 years prior to screening).

End point type	Other pre-specified

End point timeframe:

Baseline up to Week 16 (follow-up visit)

Notes:

[13] - 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: No statistical analysis was planned for this safety endpoint. Safety data were summarized

using Sponsor Data Standards.

End point values	PF-04634817 200 mg/150 mg Daily	Placebo Daily		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	167	53		
Units: subjects	154	49		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Number of Subjects With Potentially Clinically Significant Electrocardiogram (ECG) Findings

End point title	Number of Subjects With Potentially Clinically Significant Electrocardiogram (ECG) Findings[14]

End point description:

Criteria for potentially clinically important ECG values were defined as: PR interval >=300 milliseconds (msec) or >=25%/50% increase when baseline is >200 msec and ≥50% increase when baseline is less than or equal to (<=)200 msec; QRS interval >=140 msec or >=50% increase from baseline (IFB); QTc >=450 msec or >=30 msec increase; corrected QT interval using Fridericia's formula (QTcF) >=450 msec or >=30 msec increase.

End point type	Other pre-specified

End point timeframe:

Baseline, Weeks 1, 4 and 12

Notes:

[14] - 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: No statistical analysis was planned for this safety endpoint. Safety data were summarized using Sponsor Data Standards.

End point values	PF-04634817 200 mg/150 mg Daily	Placebo Daily		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	170	56		
Units: subjects				
Maximum PR Interval >=300 msec (n=164,55)	3	0		
Maximum QRS Complex >=140 msec (n=169,56)	2	1		
Maximum QT Interval >=500 msec (n=169,56)	0	0		
Maximum QTc Interval 450-<480 msec (n=169,56)	23	11		
Maximum QTc Interval 480-<500 msec (n=169,56)	4	1		
Maximum QTc Interval >=500 msec (n=169,56)	0	0		
Maximum QTcF Interval 450-<480 msec (n=169,56)	11	5		

Maximum QTcF Interval 480-<500 msec (n=169,56)	1	1		
Maximum QTcF Interval >=500 msec (n=169,56)	1	0		
PR Interval >=25/50% IFB (n=163,53)	3	0		
QRS Complex >=50% IFB (n=169,55)	3	0		
QTc Interval 30-<60 msec IFB (n=169,55)	15	4		
QTc Interval >=60 msec IFB (n=169,55)	0	0		
QTcF Interval 30-<60 msec IFB (n=169,55)	8	3		
QTcF Interval >=60 msec IFB (n=169,55)	1	0		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Number of Subjects With Treatment-Emergent Adverse Events (AEs) or Serious Adverse Events (SAEs)

End point title	Number of Subjects With Treatment-Emergent Adverse Events (AEs) or Serious Adverse Events (SAEs)[15]

End point description:

An AE was any untoward medical occurrence without regard to causality in a participant who received study drug. A 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 are events between first dose of treatment and up to 28 days after last dose that were absent before treatment or that worsened relative to pretreatment state. AEs included both SAEs and non-serious AEs.

End point type	Other pre-specified

End point timeframe:

Baseline up to 28 days after last study drug administration

Notes:

[15] - 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: No statistical analysis was planned for this safety endpoint. Safety data were summarized using Sponsor Data Standards.

End point values	PF-04634817 200 mg/150 mg Daily	Placebo Daily		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	170	56		
Units: subjects				
Adverse Events	106	36		
Serious Adverse Events	17	5		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Number of Subjects With Increased Fasting Blood Glucose

End point title	Number of Subjects With Increased Fasting Blood Glucose[16]

End point description:

End point type	Other pre-specified

End point timeframe:

Baseline up to Week 16 (follow-up visit)

Notes:

[16] - 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: No statistical analysis was planned for this safety endpoint. Safety data were summarized using Sponsor Data Standards.

End point values	PF-04634817 200 mg/150 mg Daily	Placebo Daily		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	167	53		
Units: subjects	1	0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline up to 28 days after last study drug administration

Adverse event reporting additional description:

The same event may appear as both an AE and a SAE. However, what is presented are distinct events. An event may be categorized as serious in one subject and as non-serious in another subject, or one subject may have experienced both a serious and non-serious event during the study.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups

Reporting group title	PF-04634817 150 mg

Reporting group description:

Subjects with estimated glomerular filtration rate (eGFR) values of 20 to less than (<)30 milliliters/minute (mL/min)/1.73 square meter (m^2) were dosed orally at 150 mg once daily for 12 weeks.

Reporting group title	Placebo

Reporting group description:

Subjects were dosed orally with matching placebo tablets once daily for 12 weeks.

Reporting group title	PF-04634817 200 mg

Reporting group description:

Subjects with eGFR values of 30 to 75 mL/min/1.73 m^2 were dosed orally at 200 mg once daily for 12 weeks.

Serious adverse events	PF-04634817 150 mg	Placebo	PF-04634817 200 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 30 (20.00%)	5 / 56 (8.93%)	11 / 140 (7.86%)
number of deaths (all causes)	0	1	0
number of deaths resulting from adverse events	0	0	0
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 30 (0.00%)	0 / 56 (0.00%)	1 / 140 (0.71%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 30 (0.00%)	0 / 56 (0.00%)	2 / 140 (1.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Generalised oedema			
subjects affected / exposed	0 / 30 (0.00%)	0 / 56 (0.00%)	1 / 140 (0.71%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	0 / 30 (0.00%)	0 / 56 (0.00%)	1 / 140 (0.71%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Social circumstances			
Homicide			
subjects affected / exposed	0 / 30 (0.00%)	1 / 56 (1.79%)	0 / 140 (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
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 30 (0.00%)	1 / 56 (1.79%)	0 / 140 (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
Cardiac disorders			
Cardiac failure			
subjects affected / exposed	1 / 30 (3.33%)	0 / 56 (0.00%)	0 / 140 (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
Nervous system disorders			
Cerebral infarction			
subjects affected / exposed	0 / 30 (0.00%)	0 / 56 (0.00%)	1 / 140 (0.71%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dizziness			
subjects affected / exposed	1 / 30 (3.33%)	0 / 56 (0.00%)	0 / 140 (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
Gastrointestinal disorders			
Gastritis			

subjects affected / exposed	0 / 30 (0.00%)	0 / 56 (0.00%)	1 / 140 (0.71%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis acute			
subjects affected / exposed	0 / 30 (0.00%)	0 / 56 (0.00%)	1 / 140 (0.71%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	0 / 30 (0.00%)	0 / 56 (0.00%)	1 / 140 (0.71%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Dermatitis			
subjects affected / exposed	1 / 30 (3.33%)	0 / 56 (0.00%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Erythrodermic psoriasis			
subjects affected / exposed	1 / 30 (3.33%)	0 / 56 (0.00%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Renal failure acute			
subjects affected / exposed	2 / 30 (6.67%)	0 / 56 (0.00%)	2 / 140 (1.43%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Gouty arthritis			
subjects affected / exposed	1 / 30 (3.33%)	0 / 56 (0.00%)	0 / 140 (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
Infections and infestations			
Cellulitis			

subjects affected / exposed	0 / 30 (0.00%)	1 / 56 (1.79%)	0 / 140 (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
Localised infection			
subjects affected / exposed	0 / 30 (0.00%)	1 / 56 (1.79%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	2 / 30 (6.67%)	1 / 56 (1.79%)	1 / 140 (0.71%)
occurrences causally related to treatment / all	1 / 2	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic shock			
subjects affected / exposed	1 / 30 (3.33%)	0 / 56 (0.00%)	0 / 140 (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
Viral infection			
subjects affected / exposed	0 / 30 (0.00%)	0 / 56 (0.00%)	1 / 140 (0.71%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 30 (3.33%)	0 / 56 (0.00%)	0 / 140 (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
Hypokalaemia			
subjects affected / exposed	1 / 30 (3.33%)	0 / 56 (0.00%)	0 / 140 (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

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	PF-04634817 150 mg	Placebo	PF-04634817 200 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	11 / 30 (36.67%)	15 / 56 (26.79%)	40 / 140 (28.57%)
Investigations			
Gamma-glutamyltransferase increased			
subjects affected / exposed	2 / 30 (6.67%)	0 / 56 (0.00%)	1 / 140 (0.71%)
occurrences (all)	2	0	1
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 30 (3.33%)	3 / 56 (5.36%)	6 / 140 (4.29%)
occurrences (all)	2	3	6
Nervous system disorders			
Dizziness			
subjects affected / exposed	2 / 30 (6.67%)	1 / 56 (1.79%)	4 / 140 (2.86%)
occurrences (all)	2	1	7
General disorders and administration site conditions			
Oedema peripheral			
subjects affected / exposed	3 / 30 (10.00%)	4 / 56 (7.14%)	8 / 140 (5.71%)
occurrences (all)	3	4	9
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	2 / 30 (6.67%)	3 / 56 (5.36%)	12 / 140 (8.57%)
occurrences (all)	2	3	12
Nausea			
subjects affected / exposed	2 / 30 (6.67%)	2 / 56 (3.57%)	5 / 140 (3.57%)
occurrences (all)	2	2	7
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	2 / 30 (6.67%)	1 / 56 (1.79%)	0 / 140 (0.00%)
occurrences (all)	2	1	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	2 / 30 (6.67%)	1 / 56 (1.79%)	2 / 140 (1.43%)
occurrences (all)	2	1	2
Infections and infestations			

Nasopharyngitis			
subjects affected / exposed	2 / 30 (6.67%)	3 / 56 (5.36%)	6 / 140 (4.29%)
occurrences (all)	2	3	8
Upper respiratory tract infection			
subjects affected / exposed	2 / 30 (6.67%)	2 / 56 (3.57%)	5 / 140 (3.57%)
occurrences (all)	2	2	6
Metabolism and nutrition disorders			
Hyperkalaemia			
subjects affected / exposed	2 / 30 (6.67%)	1 / 56 (1.79%)	1 / 140 (0.71%)
occurrences (all)	2	1	1
Hypoglycaemia			
subjects affected / exposed	2 / 30 (6.67%)	1 / 56 (1.79%)	2 / 140 (1.43%)
occurrences (all)	3	1	3

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 October 2012	Electrocardiogram (ECG) assessments were modified and guidance on participant withdrawal ("stopping rules") was included as requested by the Food and Drug Administration (FDA). Exclusion criterion was loosened to exclude subjects with a history of proteinuria >8.5 g/day.
27 September 2013	Dose adjustment to 150 mg once daily (QD) in subjects with eGFR <30 mL/min.1.73 m^2 was added. Screening window was extended to 35 days to accomodate additional TB testing and chest X-ray if necessary. Inclusion criterion for eGFR was changed from 30-59 mL/min/1.73 m^2 to 20-75 mL/min/1.73 m^2 based on the results from a previous study. Inclusion criterion of UPCR >=390 mg/g was removed. Lifestyle guidelines relating to condom use by male subjects was removed.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported