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 PHOSPHODIESTERASE 5 INHIBITOR (PF-00489791) IN ADULTS WITH TYPE 2 DIABETES AND OVERT NEPHROPATHY

Summary

EudraCT number	2010-021358-20
Trial protocol	GB PL SK SE DK
Global end of trial date	12 August 2013

Results information

Result version number	v1 (current)
This version publication date	01 April 2016
First version publication date	29 July 2015

Trial information

Trial identification

Sponsor protocol code	A7331011

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01200394
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Pfizer Inc.
Sponsor organisation address	235 E 42nd Street, New York, United States, NY 10017
Public contact	Clinical Trials.gov Call Center, Pfizer Inc., 1-800- 718-1021, ClinicalTrials.gov_Inquiries@pfizer.com
Scientific contact	Clinical Trials.gov Call Center, Pfizer Inc., 1-800- 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	24 March 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	12 August 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of PF-00489791 in the reduction of albuminuria in subjects with type 2 diabetes and overt nephropathy.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and in compliance with all International Conference on Harmonization (ICH) Good Clinical Practice (GCP) Guidelines. All the local regulatory requirements pertinent to safety of trial subjects were followed.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	17 December 2010
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	Australia: 5
Country: Number of subjects enrolled	Canada: 25
Country: Number of subjects enrolled	Hong Kong: 19
Country: Number of subjects enrolled	India: 21
Country: Number of subjects enrolled	Korea, Republic of: 22
Country: Number of subjects enrolled	Malaysia: 29
Country: Number of subjects enrolled	Mexico: 13
Country: Number of subjects enrolled	Poland: 8
Country: Number of subjects enrolled	Serbia: 31
Country: Number of subjects enrolled	Slovakia: 1
Country: Number of subjects enrolled	South Africa: 12
Country: Number of subjects enrolled	Sweden: 2
Country: Number of subjects enrolled	United Kingdom: 4
Country: Number of subjects enrolled	United States: 64
Worldwide total number of subjects	256
EEA total number of subjects	15

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)	155
From 65 to 84 years	101
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Study was started on 17 December 2010 and ended on 12 August 2013. Overall, 256 subjects were enrolled into the study across 14 countries.

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?	Yes
Arm title	Placebo

Arm description:

Placebo matched to PF-00489791 tablet once daily for 12 weeks.

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

Dosage and administration details:

Subjects received Placebo matched to PF-00489791 tablet once daily for 12 weeks. Each daily dose comprised of two 10 milligram (mg) tablets of placebo.

Arm title	PF-00489791 20 mg

Arm description:

PF-00489791 tablet once daily for 12 weeks.

Arm type	Experimental
Investigational medicinal product name	PF-00489791
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received PF-00489791 20 mg tablet once daily for 12 weeks. Each daily dose comprised of two 10 mg tablets of PF-00489791.

Number of subjects in period 1	Placebo	PF-00489791 20 mg
Started	64	192
Completed	62	164
Not completed	2	28
'Protocol Violation '	-	3
Consent withdrawn by subject	-	5
Did not meet entrance criteria	1	4
Adverse Event	-	14
'Death '	1	-
'Unspecified '	-	1
Lost to follow-up	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Placebo matched to PF-00489791 tablet once daily for 12 weeks.	
Reporting group title	PF-00489791 20 mg
Reporting group description:	
PF-00489791 tablet once daily for 12 weeks.	

Reporting group values	Placebo	PF-00489791 20 mg	Total
Number of subjects	64	192	256
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	59.8	62	
standard deviation	± 11	± 8.8	-
Gender categorical Units: Subjects			
Female	13	48	61
Male	51	144	195

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Placebo matched to PF-00489791 tablet once daily for 12 weeks.	
Reporting group title	PF-00489791 20 mg
Reporting group description:	
PF-00489791 tablet once daily for 12 weeks.	

Primary: Change From Baseline in Urinary Albumin Creatinine Ratio (UACR) at Week 12

End point title	Change From Baseline in Urinary Albumin Creatinine Ratio (UACR) at Week 12
End point description:	
UACR is a ratio between 2 measured substances in urine: milligram of albumin per millimole (mmol) of creatinine. A decrease in UACR may be associated with improved renal and cardiovascular function. The mean values of the 3 consecutive first morning void urine samples (obtained 2 days prior to, and with last sample collected on the morning of scheduled clinic visit) were used to determine UACR at the scheduled clinic visit. The mean values of the 3 consecutive first morning void urine samples obtained at screening were used to determine baseline UACR. Full analysis set (FAS) was performed for this endpoint. Full analysis set included all randomized subjects who received at least 1 dose of study medication and had at least 1 post-dose efficacy measurement. Here 'n' signifies subjects evaluable at specified time point.	
End point type	Primary
End point timeframe:	
Baseline, Week 12	

End point values	Placebo	PF-00489791 20 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	64	192		
Units: milligram per millimole (mg/mmol)				
arithmetic mean (standard deviation)				
Baseline (n = 63, 191)	195.13 (± 171.8116)	182.378 (± 156.5097)		
Change at Week 12 (n = 60, 164)	9.072 (± 176.436)	-6.539 (± 128.4866)		

Statistical analyses

Statistical analysis title	Week 12: 0 percent (%) reduction in UACR

Statistical analysis description:

Analysis of covariance (ANCOVA) model within an outlier robust Bayesian framework on normal logarithmic scale with treatment as fixed effect, baseline UACR and baseline supine systolic blood pressure (BP) as covariate. Values were back transformed from log scale. Model used informative prior distribution for placebo.

Comparison groups	Placebo v PF-00489791 20 mg
Number of subjects included in analysis	256
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.9889 [2]
Method	ANCOVA
Parameter estimate	Geometric Mean Ratio
Point estimate	0.843
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.728
upper limit	0.975

Notes:

[1] - Bayesian Design was used in the study.

[2] - Posterior distribution was used to calculate a posterior probability (presented as p-value) that PF-00489791 has a greater than 0 percent (%) reduction in UACR compared to placebo.

Statistical analysis title	Week 12: 20% reduction in UACR

Statistical analysis description:

ANCOVA model within an outlier robust Bayesian framework on normal logarithmic scale with treatment as fixed effect, baseline UACR and baseline supine systolic BP as covariate. Values were back transformed from log scale. Model used informative prior distribution for placebo.

Comparison groups	Placebo v PF-00489791 20 mg
Number of subjects included in analysis	256
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	= 0.2402 [4]
Method	ANCOVA

Notes:

[3] - Bayesian Design was used in the study.

[4] - Posterior distribution was used to calculate a posterior probability (presented as p-value) that PF-00489791 has a greater than 0 percent (%) reduction in UACR compared to placebo.

Secondary: Change From Baseline in Urinary Albumin Creatinine Ratio (UACR) at Week 3, 6 and 16

End point title	Change From Baseline in Urinary Albumin Creatinine Ratio (UACR) at Week 3, 6 and 16

End point description:

UACR is a ratio between 2 measured substances in urine: milligram of albumin per mmol of creatinine. A decrease in UACR may be associated with improved renal and cardiovascular function. The mean values of the 3 consecutive first morning void urine samples (obtained 2 days prior to, and with last sample collected on the morning of scheduled clinic visit) were used to determine UACR at the scheduled clinic visit. The mean values of the 3 consecutive first morning void urine samples obtained at screening were used to determine baseline UACR. Full analysis set included all randomized subjects who received at least 1 dose of study medication and had at least 1 post-dose efficacy measurement. Here 'n' signifies subjects evaluable at specified time point for each arm, respectively.

End point type	Secondary

End point timeframe:

Baseline, Week 3, 6, 16 (follow-up)

End point values	Placebo	PF-00489791 20 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	64	192		
Units: mg/mmol				
arithmetic mean (standard deviation)				
Change at Week 3 (n = 60, 171)	-11.805 (± 161.7282)	-14.268 (± 94.8469)		
Change at Week 6 (n = 62, 171)	-7.772 (± 162.0838)	-2.546 (± 179.5896)		
Change at Week 16 (n = 60, 162)	16.5 (± 202.76)	2.802 (± 107.9582)		

Statistical analyses

Statistical analysis title	Week 3

Statistical analysis description:

Mixed model repeated measures (MMRM) on normal logarithmic scale with baseline, baseline supine systolic BP, visit, treatment, baseline by visit interaction and treatment by visit interaction as fixed effects. Unstructured covariance matrix was used to estimate variances and covariance within subject across time points. Values were back-transformed from log scale.

Comparison groups	Placebo v PF-00489791 20 mg
Number of subjects included in analysis	256
Analysis specification	Pre-specified
Analysis type	superiority[5]
P-value	= 0.0382
Method	Mixed models analysis
Parameter estimate	Geometric Mean Ratio
Point estimate	0.8759
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.7727
upper limit	0.9927

Notes:

[5] - Sensitivity analysis was used for this endpoint.

Statistical analysis title	Week 6

Statistical analysis description:

MMRM on normal logarithmic scale with baseline, baseline supine systolic BP, visit, treatment, baseline by visit interaction and treatment by visit interaction as fixed effects. Unstructured covariance matrix was used to estimate variances and covariance within subject across time points. Values were back-transformed from log scale.

Comparison groups	Placebo v PF-00489791 20 mg
Number of subjects included in analysis	256
Analysis specification	Pre-specified
Analysis type	superiority[6]
P-value	= 0.0112
Method	Mixed models analysis
Parameter estimate	Geometric Mean Ratio
Point estimate	0.8311

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.7208
upper limit	0.9584

Notes:

[6] - Sensitivity analysis was used for this endpoint.

Statistical analysis title	Week 16

Statistical analysis description:

MMRM on normal logarithmic scale with baseline, baseline supine systolic BP, visit, treatment, baseline by visit interaction and treatment by visit interaction as fixed effects. Unstructured covariance matrix was used to estimate variances and covariance within subject across time points. Values were back-transformed from log scale.

Comparison groups	Placebo v PF-00489791 20 mg
Number of subjects included in analysis	256
Analysis specification	Pre-specified
Analysis type	superiority[7]
P-value	= 0.149
Method	Mixed models analysis
Parameter estimate	Geometric Mean Ratio
Point estimate	0.8816
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.7427
upper limit	1.0465

Notes:

[7] - Sensitivity analysis was used for this endpoint.

Secondary: Change From Baseline in Urinary Protein Creatinine Ratio (UPCR) at Week 3, 6, 12, and 16

End point title	Change From Baseline in Urinary Protein Creatinine Ratio (UPCR) at Week 3, 6, 12, and 16

End point description:

UPCR is a ratio between two measured substances in urine: milligram of protein per millimole (mmol) of creatinine. A decrease in UPCR may be associated with improved renal and cardiovascular function. The mean values of the 3 consecutive first morning void urine samples (obtained 2 days prior to, and with last sample collected on the morning of scheduled clinic visit) were used to determine UPCR at the scheduled clinic visit. The mean values of the 3 consecutive first morning void urine samples obtained at screening were used to determine baseline UPCR. Full analysis set included all randomized subjects who received at least 1 dose of study medication and had at least 1 post-dose efficacy measurement. Here 'n' signifies subjects evaluable at specified time point for each arm, respectively.

End point type	Secondary

End point timeframe:

Baseline, Week 3, 6, 12, 16 (follow-up)

End point values	Placebo	PF-00489791 20 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	64	192		
Units: mg/mmol				
arithmetic mean (standard deviation)				
Baseline (n = 63, 191)	282.208 (± 259.8496)	261.015 (± 220.526)		
Change at Week 3 (n = 60, 170)	-20.302 (± 247.449)	-26.883 (± 161.0038)		
Change at Week 6 (n = 62, 170)	-10.278 (± 256.7216)	10.699 (± 290.5749)		
Change at Week 12 (n = 59, 164)	14.632 (± 283.9874)	-5.371 (± 207.3333)		
Change at Week 16 (n = 60, 162)	30.88 (± 332.0766)	20.299 (± 190.3546)		

Statistical analyses

Statistical analysis title	Week 3

Statistical analysis description:

MMRM on normal logarithmic scale with baseline, baseline supine systolic BP, visit, treatment, baseline by visit interaction and treatment by visit interaction as fixed effects. Unstructured covariance matrix was used to estimate variances and covariance within subject across time points. Values were back-transformed from log scale.

Comparison groups	Placebo v PF-00489791 20 mg
Number of subjects included in analysis	256
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0297
Method	Mixed models analysis
Parameter estimate	Geometric Mean Ratio
Point estimate	0.8565
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.745
upper limit	0.9847

Statistical analysis title	Week 6

Statistical analysis description:

MMRM on normal logarithmic scale with baseline, baseline supine systolic BP, visit, treatment, baseline by visit interaction and treatment by visit interaction as fixed effects. Unstructured covariance matrix was used to estimate variances and covariance within subject across time points. Values were back-transformed from log scale.

Comparison groups	Placebo v PF-00489791 20 mg

Number of subjects included in analysis	256
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0305
Method	Mixed models analysis
Parameter estimate	Geometric Mean Ratio
Point estimate	0.8524
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.7376
upper limit	0.985

Statistical analysis title	Week 12

Statistical analysis description:

MMRM on normal logarithmic scale with baseline, baseline supine systolic BP, visit, treatment, baseline by visit interaction and treatment by visit interaction as fixed effects. Unstructured covariance matrix was used to estimate variances and covariance within subject across time points. Values were back-transformed from log scale.

Comparison groups	Placebo v PF-00489791 20 mg
Number of subjects included in analysis	256
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0068
Method	Mixed models analysis
Parameter estimate	Geometric Mean Ratio
Point estimate	0.7937
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.6717
upper limit	0.9378

Statistical analysis title	Week 16

Statistical analysis description:

MMRM on normal logarithmic scale with baseline, baseline supine systolic BP, visit, treatment, baseline by visit interaction and treatment by visit interaction as fixed effects. Unstructured covariance matrix was used to estimate variances and covariance within subject across time points. Values were back-transformed from log scale.

Comparison groups	Placebo v PF-00489791 20 mg
Number of subjects included in analysis	256
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1151
Method	Mixed models analysis
Parameter estimate	Geometric Mean Ratio
Point estimate	0.8634

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.719
upper limit	1.0368

Secondary: Change From Baseline in Estimated Glomerular Filtration Rate (eGFR) at Week 3, 6, 12, and 16

End point title	Change From Baseline in Estimated Glomerular Filtration Rate (eGFR) at Week 3, 6, 12, and 16

End point description:

The eGFR was calculated using 4 variable formula developed by the modification of diet in renal disease (MDRD) study group. The 4 variables needed to estimate glomerular filtration rate (GFR) using this formula were serum creatinine concentration (sCr), age, sex (for females, eGFR was multiplied by 0.742) and ethnic origin (for African-Caribbean people only, eGFR was multiplied by 1.212). Thus eGFR in milliliter per minute per 1.73 square meter (mL/min/1.73 m^2) = 175*(sCr/88.4)^-1.154*(Age) ^-0.203*(0.742 if female)*(1.212 if African-Caribbean). Baseline eGFR was determined predose at Week 0 (Day 1). Full analysis set included all randomized subjects who received at least 1 dose of study medication and had at least 1 post-dose efficacy measurement. Here 'n' signifies subjects evaluable at specified time point for each arm, respectively.

End point type	Secondary

End point timeframe:

Baseline, Week 3, 6, 12, 16 (follow-up)

End point values	Placebo	PF-00489791 20 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	64	192		
Units: mL/min/1.73 m^2				
arithmetic mean (standard deviation)				
Baseline (n = 61, 188)	38.575 (± 11.9122)	37.74 (± 9.8834)		
Change at Week 3 (n = 59, 172)	0.069 (± 6.2868)	-0.156 (± 4.6044)		
Change at Week 6 (n = 59, 166)	-0.93 (± 5.3513)	-0.755 (± 5.2701)		
Change at Week 12 (n = 58, 161)	-1.435 (± 5.3757)	-1.463 (± 5.1074)		
Change at Week 16 (n = 59, 163)	-1.915 (± 5.9005)	-1.659 (± 6.0659)		

Statistical analyses

Statistical analysis title	Week 3

Statistical analysis description:

MMRM on normal logarithmic scale with change from baseline as response variable and baseline, baseline supine systolic BP, visit, treatment, baseline by visit interaction and treatment by visit interaction as fixed effects. Unstructured covariance matrix was used to estimate variances and covariance within subject across time points. Values were back-transformed from log scale.

Comparison groups	Placebo v PF-00489791 20 mg
Number of subjects included in analysis	256
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3585
Method	Mixed models analysis
Parameter estimate	Geometric Mean Ratio
Point estimate	0.9816
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.9434
upper limit	1.0214

Statistical analysis title	Week 6

Statistical analysis description:

MMRM on normal logarithmic scale with change from baseline as response variable and baseline, baseline supine systolic BP, visit, treatment, baseline by visit interaction and treatment by visit interaction as fixed effects. Unstructured covariance matrix was used to estimate variances and covariance within subject across time points. Values were back-transformed from log scale.

Comparison groups	Placebo v PF-00489791 20 mg
Number of subjects included in analysis	256
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7475
Method	Mixed models analysis
Parameter estimate	Geometric Mean Ratio
Point estimate	0.9939
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.9577
upper limit	1.0315

Statistical analysis title	Week 12

Statistical analysis description:

MMRM on normal logarithmic scale with change from baseline as response variable and baseline, baseline supine systolic BP, visit, treatment, baseline by visit interaction and treatment by visit interaction as fixed effects. Unstructured covariance matrix was used to estimate variances and covariance within subject across time points. Values were back-transformed from log scale.

Comparison groups	Placebo v PF-00489791 20 mg
Number of subjects included in analysis	256
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4972
Method	Mixed models analysis
Parameter estimate	Geometric Mean Ratio
Point estimate	0.9866

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.9488
upper limit	1.0259

Statistical analysis title	Week 16

Statistical analysis description:

MMRM on normal logarithmic scale with change from baseline as response variable and baseline, baseline supine systolic BP, visit, treatment, baseline by visit interaction and treatment by visit interaction as fixed effects. Unstructured covariance matrix was used to estimate variances and covariance within subject across time points. Values were back-transformed from log scale.

Comparison groups	Placebo v PF-00489791 20 mg
Number of subjects included in analysis	256
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9146
Method	Mixed models analysis
Parameter estimate	Geometric Mean Ratio
Point estimate	1.0024
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.9588
upper limit	1.0481

Secondary: Systolic, Diastolic and Mean Blood Pressure at Week 0, 3, 6, 12, and 16

End point title	Systolic, Diastolic and Mean Blood Pressure at Week 0, 3, 6, 12, and 16

End point description:

Systolic Blood Pressure (SBP) is the blood pressure (pressure exerted by circulating blood on the walls of blood vessels) when heart is contracting; it is the maximum arterial pressure during contraction of left ventricle of heart. Diastolic Blood Pressure (DBP) is the blood pressure (pressure exerted by circulating blood on the walls of blood vessels) when heart is relaxing; it is the minimum arterial pressure during relaxation and dilation of ventricles of heart. Mean blood pressure (MBP) = diastolic blood pressure + ([systolic blood pressure - diastolic blood pressure]/3). After a minimum of 5 minutes of rest, supine BP was measured with the subject's arm supported at the level of the heart. Full analysis set included all randomized subjects who received at least 1 dose of study medication and had at least 1 post-dose efficacy measurement.

End point type	Secondary

End point timeframe:

Week 0, 3, 6, 12, 16 (follow-up)

End point values	Placebo	PF-00489791 20 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	64	192		
Units: millimeter of mercury (mmHg)				
least squares mean (confidence interval 95%)				
Supine Systolic BP, Week 0	137.2 (135.01 to 139.4)	131.81 (130.53 to 133.1)		
Supine Diastolic BP, Week 0	76.98 (75.53 to 78.42)	73.27 (72.43 to 74.11)		
Supine Mean BP, Week 0	107.27 (105.66 to 108.88)	102.68 (101.74 to 103.62)		
Supine Systolic BP, Week 3	136.68 (134.3 to 139.05)	136.15 (134.74 to 137.56)		
Supine Diastolic BP, Week 3	76.78 (75.25 to 78.31)	77.18 (76.27 to 78.1)		
Supine Mean BP, Week 3	107.06 (105.32 to 108.8)	106.9 (105.86 to 107.94)		
Supine Systolic BP, Week 6	137.41 (134.9 to 139.93)	136.94 (135.42 to 138.45)		
Supine Diastolic BP, Week 6	76.88 (75.32 to 78.43)	76.41 (75.48 to 77.35)		
Supine Mean BP, Week 6	107.37 (105.58 to 109.15)	106.7 (105.62 to 107.77)		
Supine Systolic BP, Week 12	136.89 (133.73 to 140.06)	137.7 (135.79 to 139.6)		
Supine Diastolic BP, Week 12	77.32 (75.51 to 79.13)	76.69 (75.61 to 77.78)		
Supine Mean BP, Week 12	107.41 (105.27 to 109.55)	107.14 (105.85 to 108.42)		
Supine Systolic BP, Week 16	138.38 (135.51 to 141.25)	138.89 (137.15 to 140.63)		
Supine Diastolic BP, Week 16	77.25 (75.59 to 78.92)	77.9 (76.9 to 78.91)		
Supine Mean BP, Week 16	108 (106.1 to 109.91)	108.47 (107.31 to 109.62)		

Statistical analyses

Statistical analysis title	Supine Systolic BP, Week 0

Statistical analysis description:

MMRM model included baseline, visit, treatment, baseline by visit interaction and treatment by visit interaction as fixed effects. The unstructured covariance matrix was used to estimate variances and covariance within subject across time points.

Comparison groups	Placebo v PF-00489791 20 mg

Number of subjects included in analysis	256
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Least Squares (LS) Mean Difference
Point estimate	-5.39
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.94
upper limit	-2.84
Variability estimate	Standard error of the mean
Dispersion value	1.2942

Statistical analysis title	Supine Diastolic BP, Week 0

Statistical analysis description:

MMRM model included baseline, visit, treatment, baseline by visit interaction and treatment by visit interaction as fixed effects. The unstructured covariance matrix was used to estimate variances and covariance within subject across time points.

Comparison groups	Placebo v PF-00489791 20 mg
Number of subjects included in analysis	256
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-3.71
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.38
upper limit	-2.04
Variability estimate	Standard error of the mean
Dispersion value	0.849

Statistical analysis title	Supine Mean BP, Week 0

Statistical analysis description:

MMRM model included baseline, visit, treatment, baseline by visit interaction and treatment by visit interaction as fixed effects. The unstructured covariance matrix was used to estimate variances and covariance within subject across time points.

Comparison groups	Placebo v PF-00489791 20 mg

Number of subjects included in analysis	256
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-4.59
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.46
upper limit	-2.72
Variability estimate	Standard error of the mean
Dispersion value	0.9489

Statistical analysis title	Supine Systolic BP, Week 3

Statistical analysis description:

MMRM model included baseline, visit, treatment, baseline by visit interaction and treatment by visit interaction as fixed effects. The unstructured covariance matrix was used to estimate variances and covariance within subject across time points.

Comparison groups	Placebo v PF-00489791 20 mg
Number of subjects included in analysis	256
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7093
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-0.52
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.29
upper limit	2.24
Variability estimate	Standard error of the mean
Dispersion value	1.4056

Statistical analysis title	Supine Diastolic BP, Week 3

Statistical analysis description:

MMRM model included baseline, visit, treatment, baseline by visit interaction and treatment by visit interaction as fixed effects. The unstructured covariance matrix was used to estimate variances and covariance within subject across time points.

Comparison groups	Placebo v PF-00489791 20 mg

Number of subjects included in analysis	256
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6564
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.39
upper limit	2.2
Variability estimate	Standard error of the mean
Dispersion value	0.9089

Statistical analysis title	Supine Mean BP, Week 3

Statistical analysis description:

MMRM model included baseline, visit, treatment, baseline by visit interaction and treatment by visit interaction as fixed effects. The unstructured covariance matrix was used to estimate variances and covariance within subject across time points.

Comparison groups	Placebo v PF-00489791 20 mg
Number of subjects included in analysis	256
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8763
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-0.16
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.2
upper limit	1.87
Variability estimate	Standard error of the mean
Dispersion value	1.0334

Statistical analysis title	Supine Systolic BP, Week 6

Statistical analysis description:

MMRM model included baseline, visit, treatment, baseline by visit interaction and treatment by visit interaction as fixed effects. The unstructured covariance matrix was used to estimate variances and covariance within subject across time points.

Comparison groups	Placebo v PF-00489791 20 mg

Number of subjects included in analysis	256
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7491
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-0.48
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.42
upper limit	2.46
Variability estimate	Standard error of the mean
Dispersion value	1.4926

Statistical analysis title	Supine Diastolic BP, Week 6

Statistical analysis description:

MMRM model included baseline, visit, treatment, baseline by visit interaction and treatment by visit interaction as fixed effects. The unstructured covariance matrix was used to estimate variances and covariance within subject across time points.

Comparison groups	Placebo v PF-00489791 20 mg
Number of subjects included in analysis	256
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6141
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-0.47
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.29
upper limit	1.35
Variability estimate	Standard error of the mean
Dispersion value	0.9235

Statistical analysis title	Supine Mean BP, Week 6

Statistical analysis description:

MMRM model included baseline, visit, treatment, baseline by visit interaction and treatment by visit interaction as fixed effects. The unstructured covariance matrix was used to estimate variances and covariance within subject across time points.

Comparison groups	Placebo v PF-00489791 20 mg

Number of subjects included in analysis	256
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5281
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-0.67
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.75
upper limit	1.42
Variability estimate	Standard error of the mean
Dispersion value	1.0582

Statistical analysis title	Supine Systolic BP, Week 12

Statistical analysis description:

MMRM model included baseline, visit, treatment, baseline by visit interaction and treatment by visit interaction as fixed effects. The unstructured covariance matrix was used to estimate variances and covariance within subject across time points.

Comparison groups	Placebo v PF-00489791 20 mg
Number of subjects included in analysis	256
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6695
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	0.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.9
upper limit	4.5
Variability estimate	Standard error of the mean
Dispersion value	1.8764

Statistical analysis title	Supine Diastolic BP, Week 12

Statistical analysis description:

MMRM model included baseline, visit, treatment, baseline by visit interaction and treatment by visit interaction as fixed effects. The unstructured covariance matrix was used to estimate variances and covariance within subject across time points.

Comparison groups	Placebo v PF-00489791 20 mg

Number of subjects included in analysis	256
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5607
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-0.63
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.74
upper limit	1.49
Variability estimate	Standard error of the mean
Dispersion value	1.073

Statistical analysis title	Supine Mean BP, Week 12

Statistical analysis description:

MMRM model included baseline, visit, treatment, baseline by visit interaction and treatment by visit interaction as fixed effects. The unstructured covariance matrix was used to estimate variances and covariance within subject across time points.

Comparison groups	Placebo v PF-00489791 20 mg
Number of subjects included in analysis	256
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8297
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-0.27
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.78
upper limit	2.23
Variability estimate	Standard error of the mean
Dispersion value	1.2722

Statistical analysis title	Supine Systolic BP, Week 16

Statistical analysis description:

MMRM model included baseline, visit, treatment, baseline by visit interaction and treatment by visit interaction as fixed effects. The unstructured covariance matrix was used to estimate variances and covariance within subject across time points.

Comparison groups	Placebo v PF-00489791 20 mg

Number of subjects included in analysis	256
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7644
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	0.51
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.85
upper limit	3.87
Variability estimate	Standard error of the mean
Dispersion value	1.7065

Statistical analysis title	Supine Diastolic BP, Week 16

Statistical analysis description:

MMRM model included baseline, visit, treatment, baseline by visit interaction and treatment by visit interaction as fixed effects. The unstructured covariance matrix was used to estimate variances and covariance within subject across time points.

Comparison groups	Placebo v PF-00489791 20 mg
Number of subjects included in analysis	256
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5123
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	0.65
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.3
upper limit	2.61
Variability estimate	Standard error of the mean
Dispersion value	0.9917

Statistical analysis title	Supine Mean BP, Week 16

Statistical analysis description:

MMRM model included baseline, visit, treatment, baseline by visit interaction and treatment by visit interaction as fixed effects. The unstructured covariance matrix was used to estimate variances and covariance within subject across time points.

Comparison groups	Placebo v PF-00489791 20 mg

Number of subjects included in analysis	256
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6838
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	0.46
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.77
upper limit	2.7
Variability estimate	Standard error of the mean
Dispersion value	1.1355

Secondary: Change From Baseline in Serum Creatinine Concentration at Week 3, 6, 12, and 16

End point title	Change From Baseline in Serum Creatinine Concentration at Week 3, 6, 12, and 16

End point description:

Serum creatinine concentration was used as a marker of renal function. Baseline serum creatinine concentration was determined predose at Week 0 (Day 1). Full analysis set included all randomized subjects who received at least 1 dose of study medication and had at least 1 post-dose efficacy measurement. Here 'n' signifies subjects evaluable at specified time point for each arm, respectively.

End point type	Secondary

End point timeframe:

Baseline, Week 3, 6, 12, 16 (follow-up)

End point values	Placebo	PF-00489791 20 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	64	192		
Units: micromole per liter (mcmol/L)				
arithmetic mean (standard deviation)				
Baseline (n = 61, 188)	164.929 (± 42.0837)	163.637 (± 42.9529)		
Change at Week 3 (n = 59, 172)	1.232 (± 23.9961)	2.691 (± 20.6884)		
Change at Week 6 (n = 59, 166)	3.158 (± 18.0835)	4.974 (± 21.7977)		
Change at Week 12 (n = 58, 161)	6.139 (± 20.7198)	8.11 (± 22.3709)		
Change at Week 16 (n = 59, 163)	11.527 (± 28.5175)	9.269 (± 26.647)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Urine Transforming Growth Factor (TGF) Beta-1 Concentration at Week 3, 6, 12, and 16

End point title	Change From Baseline in Urine Transforming Growth Factor (TGF) Beta-1 Concentration at Week 3, 6, 12, and 16

End point description:

TGF Beta-1 is a major fibrogenic growth factor implicated in the pathogenesis of renal scarring. It is overexpressed in the diabetic kidney where it may promote matrix accumulation. Baseline TGF Beta-1 concentration was determined predose at Week 0 (Day 1). Full analysis set included all randomized subjects who received at least 1 dose of study medication and had at least 1 post-dose efficacy measurement. Here 'n' signifies subjects evaluable at specified time point for each arm, respectively.

End point type	Secondary

End point timeframe:

Baseline, Week 3, 6, 12, 16 (follow-up)

End point values	Placebo	PF-00489791 20 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	64	192		
Units: picogram per milliliter (pg/mL)				
arithmetic mean (standard deviation)				
Baseline (n = 55, 159)	177.88 (± 231.154)	213.37 (± 274.409)		
Change at Week 3 (n = 52, 145)	-22.81 (± 260.14)	-54.06 (± 349.817)		
Change at Week 6 (n = 53, 141)	23.33 (± 345.304)	-68.59 (± 333.378)		
Change at Week 12 (n = 49, 136)	-36.2 (± 281.523)	-11.87 (± 328.482)		
Change at Week 16 (n = 49, 125)	-23.54 (± 134.752)	-31.32 (± 299.546)		

Statistical analyses

Statistical analysis title	Week 3

Statistical analysis description:

MMRM on normal logarithmic scale with change from baseline as response variable and baseline, baseline supine systolic BP, visit, treatment, baseline by visit interaction and treatment by visit interaction as fixed effects. Unstructured covariance matrix was used to estimate variances and covariance within subject across time points. Values were back-transformed from log scale.

Comparison groups	Placebo v PF-00489791 20 mg
Number of subjects included in analysis	256
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5422
Method	Mixed models analysis
Parameter estimate	Geometric Mean Ratio
Point estimate	0.9282

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.7297
upper limit	1.1807

Statistical analysis title	Week 6

Statistical analysis description:

MMRM on normal logarithmic scale with change from baseline as response variable and baseline, baseline supine systolic BP, visit, treatment, baseline by visit interaction and treatment by visit interaction as fixed effects. Unstructured covariance matrix was used to estimate variances and covariance within subject across time points. Values were back-transformed from log scale.

Comparison groups	Placebo v PF-00489791 20 mg
Number of subjects included in analysis	256
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.049
Method	Mixed models analysis
Parameter estimate	Geometric Mean Ratio
Point estimate	0.7998
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.6402
upper limit	0.999

Statistical analysis title	Week 12

Statistical analysis description:

MMRM on normal logarithmic scale with change from baseline as response variable and baseline, baseline supine systolic BP, visit, treatment, baseline by visit interaction and treatment by visit interaction as fixed effects. Unstructured covariance matrix was used to estimate variances and covariance within subject across time points. Values were back-transformed from log scale.

Comparison groups	Placebo v PF-00489791 20 mg
Number of subjects included in analysis	256
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7264
Method	Mixed models analysis
Parameter estimate	Geometric Mean Ratio
Point estimate	1.0435
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.8211
upper limit	1.3262

Statistical analysis title	Week 16

Statistical analysis description:

MMRM on normal logarithmic scale with change from baseline as response variable and baseline, baseline supine systolic BP, visit, treatment, baseline by visit interaction and treatment by visit interaction as fixed effects. Unstructured covariance matrix was used to estimate variances and covariance within subject across time points. Values were back-transformed from log scale.

Comparison groups	Placebo v PF-00489791 20 mg
Number of subjects included in analysis	256
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3733
Method	Mixed models analysis
Parameter estimate	Geometric Mean Ratio
Point estimate	1.1154
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.8761
upper limit	1.4201

Secondary: Change From Baseline in Serum High Sensitivity C-Reactive Protein (hs-CRP) Concentration at Week 12 and 16

End point title	Change From Baseline in Serum High Sensitivity C-Reactive Protein (hs-CRP) Concentration at Week 12 and 16

End point description:

The CRP is an acute phase reactant which is virtually absent from the blood serum of healthy persons but rapidly appears in blood and body fluids in response to injurious stimuli. Baseline hs-CRP was determined predose at Week 0 (Day 1). Full analysis set included all randomized subjects who received at least 1 dose of
study medication and had at least 1 post-dose efficacy measurement. Here 'n' signifies subjects evaluable at specified time point for each arm, respectively.

End point type	Secondary

End point timeframe:

Baseline, Week 12, 16 (follow-up)

End point values	Placebo	PF-00489791 20 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	64	192		
Units: milligram per liter (mg/L)				
arithmetic mean (standard deviation)				
Baseline (n = 60, 187)	3.019 (± 3.4924)	4.33 (± 8.6809)		
Change at Week 12 (n = 56, 160)	1.183 (± 3.46)	0.106 (± 7.4909)		
Change at Week 16 (n = 57, 161)	0.317 (± 2.9508)	-0.102 (± 6.3317)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Serum Cystatin-C Concentration at Week 12 and 16

End point title	Change From Baseline in Serum Cystatin-C Concentration at Week 12 and 16

End point description:

Cystatin C is produced by all nucleated cells at a constant rate and is freely filtered at the glomerulus. The blood concentration of cystatin C depends almost entirely on the GFR and is not substantially affected by diet, nutritional status or inflammatory disease. Serum cystatin C had been proposed as an endogenous marker of GFR in subject with chronic kidney disease (CKD) than sCr. Baseline serum cystatin C was determined predose at Week 0 (Day 1). Full analysis set included all randomized subjects who received at least 1 dose of study medication and had at least 1 post-dose efficacy measurement. Here 'n' signifies subjects evaluable at specified time point for each arm, respectively.

End point type	Secondary

End point timeframe:

Baseline, Week 12, 16 (follow-up)

End point values	Placebo	PF-00489791 20 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	64	192		
Units: mg/L				
arithmetic mean (standard deviation)				
Baseline (n = 60, 188)	1.659 (± 0.4122)	1.695 (± 0.4497)		
Change at Week 12 (n = 56, 161)	0.096 (± 0.1844)	0.07 (± 0.289)		
Change at Week 16 (n = 57, 162)	0.104 (± 0.3234)	0.075 (± 0.3176)		

Statistical analyses

No statistical analyses for this end point

Secondary: Population Pharmacokinetics (PK)

End point title	Population Pharmacokinetics (PK)

End point description:

Data for this Outcome Measure are not reported here because the analysis population includes subjects who were not enrolled in this study.

End point type	Secondary

End point timeframe:

Baseline up to Week 16 (follow-up)

End point values	Placebo	PF-00489791 20 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[8]	0[9]		
Units: mg\mL				
arithmetic mean (standard deviation)	()	()		

Notes:

[8] - Data was not reported here as the analysis population includes subjects not enrolled in study.

[9] - Data was not reported here as the analysis population includes subjects not enrolled in study.

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change From Baseline in Plasma Glycosylated Hemoglobin (HbA1c) Level at Week 12 and 16

End point title	Change From Baseline in Plasma Glycosylated Hemoglobin (HbA1c) Level at Week 12 and 16

End point description:

Level of HbA1c is an indicator for the average level of blood glucose over the previous 3 months. Baseline HbA1c level was determined predose at Week 0 (Day 1). Safety analysis set (SAS) was performed for this endpoint. Safety analysis set consists of all subjects who received at least 1 dose of study medication. Here 'n' signifies subjects evaluable at specified time point for each arm, respectively.

End point type	Other pre-specified

End point timeframe:

Baseline, Week 12, 16 (follow-up)

End point values	Placebo	PF-00489791 20 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	64	192		
Units: percentage of hemoglobin				
arithmetic mean (standard deviation)				
Baseline (n = 61, 187)	7.13 (± 1.023)	7.39 (± 1.135)		
Change at Week 12 (n = 56, 157)	0.12 (± 0.856)	-0.28 (± 0.975)		
Change at Week 16 (n = 58, 161)	0.14 (± 1.009)	-0.09 (± 0.986)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Number of Subjects With Vital Signs Abnormalities

End point title	Number of Subjects With Vital Signs Abnormalities

End point description:

Criteria for determining vital signs abnormalities: supine or standing systolic BP (SBP) (less than [<] 90 mmHg and increase or decrease of greater than or equal to [>=] 30 mmHg compared to baseline value), supine or standing diastolic BP (DBP) (<50 mmHg and increase or decrease of >=20 mmHg compared to baseline value), supine pulse rate (>120 beats per minute [bpm] or <40 bpm), standing pulse rate (>140 bpm or <40 bpm). For supine, baseline was the average of the triplicate predose readings at Week 0 (Day 1). For standing, baseline is the predose reading at Week 0 (Day 1). Only subjects who met the specified criteria are reported. Safety analysis set consists of all subjects who received at least 1 dose of study medication. Here 'n' signifies subjects evaluable for specified category for each arm, respectively.

End point type	Other pre-specified

End point timeframe:

Baseline up to Week 16 (follow-up)

End point values	Placebo	PF-00489791 20 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	64	192		
Units: subjects				
Supine SBP <90 mmHg (n = 64, 192)	0	1		
Standing SBP <90 mmHg (n = 64, 189)	0	2		
Supine DBP <50 mmHg (n = 64, 192)	0	3		
Standing DBP <50 mmHg (n = 64, 189)	0	3		
Supine Pulse Rate <40 bpm (n = 64, 192)	0	1		
Increase in Supine SBP >=30 mmHg (n = 64, 192)	0	14		
Increase in Standing SBP >=30 mmHg (n = 64, 189)	1	1		
Increase in Supine DBP >=20 mmHg (n = 64, 192)	0	7		
Increase in Standing DBP >=20 mmHg (n = 64, 189)	1	0		
Decrease in Supine SBP >=30 mmHg (n = 64, 192)	0	9		
Decrease in Standing SBP >=30 mmHg (n = 64, 189)	2	11		
Decrease in Supine DBP >=20 mmHg (n = 64, 192)	0	5		
Decrease in Standing DBP >=20 mmHg (n = 64, 189)	1	11		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Number of Subjects With Edema and Fluid Overload

End point title	Number of Subjects With Edema and Fluid Overload

End point description:

Subjects were assessed for signs of edema and fluid overload. Safety analysis set consists of all subjects who received at least 1 dose of study medication.

End point type	Other pre-specified

End point timeframe:

Week 0, 3, 6, 12, 16 (follow-up)

End point values	Placebo	PF-00489791 20 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	64	192		
Units: subjects				
Week 0	0	4		
Week 3	1	8		
Week 6	1	11		
Week 12	4	9		
Week 16	5	6		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Number of Subjects With Increased Use of Diuretics

End point title	Number of Subjects With Increased Use of Diuretics

End point description:

The number of subjects, who had dose of diuretics increased during the study were reported. Safety analysis set consists of all subjects who received at least 1 dose of study medication.

End point type	Other pre-specified

End point timeframe:

Baseline up to Week 16 (follow-up)

End point values	Placebo	PF-00489791 20 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	64	192		
Units: subjects	3	10		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Number of Subjects With Laboratory Test Abnormalities

End point title	Number of Subjects With Laboratory Test Abnormalities

End point description:

Criteria for laboratory test abnormalities: Hematology (hemoglobin [<0.8*lower limit of normal{LLN}], hematocrit [<0.8*LLN], red blood cells [<0.8*LLN], platelet [<0.5*LLN/>1.75*upper limit of normal {ULN}], white blood cells [<0.6*LLN/>1.5*ULN], lymphocytes [<0.8*LLN/>1.2*ULN], neutrophils [<0.8*LLN/>1.2*ULN], basophils [>1.2*ULN], eosinophils [>1.2*ULN], monocytes [>1.2*ULN]); Liver Function (total/direct/indirect bilirubin [>1.5*ULN], aspartate aminotransferase/ alanine aminotransferase/ gamma glutamyl transpeptidase/ lactate dehydrogenase/ alkaline phosphatase [>3.0*ULN]); Renal Function (blood urea nitrogen/ creatinine [>1.3*ULN], uric acid [>1.2*ULN]); Electrolytes (sodium [<0.95*LLN/>1.05*ULN], potassium, chloride, calcium, bicarbonate [<0.9*LLN/>1.1*ULN]); Clinical Chemistry (glucose [<0.6*LLN/>1.5*ULN], glycosylated hemoglobin [>1.3*ULN], Creatine Kinase [>2.0*ULN], Amylase, Lipase[>1.5*ULN]). Safety analysis set.

End point type	Other pre-specified

End point timeframe:

Baseline up to Week 16 (follow-up)

End point values	Placebo	PF-00489791 20 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	63[10]	190[11]		
Units: subjects	62	190		

Notes:

[10] - Here 'N' (number of subjects analyzed) signifies subjects evaluable for this measure.

[11] - Here 'N' (number of subjects analyzed) signifies subjects evaluable for this measure.

Statistical analyses

No statistical analyses for this end point

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

End point title	Number of Subjects With Treatment-Emergent Adverse Events (AEs) and Serious Adverse Events (SAEs)

End point description:

An AE was any untoward medical occurrence in a subject who received study medication without regard to possibility of causal relationship. SAE: 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 study medication and up to Week 16 (follow-up) that were absent before treatment or that worsened relative to pre-treatment state. Safety analysis set consists of all subjects who received at least 1 dose of study medication.

End point type	Other pre-specified

End point timeframe:

Baseline up to Week 16 (follow-up)

End point values	Placebo	PF-00489791 20 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	64	192		
Units: subjects				
AEs	36	105		
SAEs	6	13		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AEs/SAEs: recorded from Week 0 to Week 16

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 1 subject and as nonserious in another, or 1 subject may have experienced both serious, nonserious event during study. EU BR specific AE tables were generated separately as per EU format using latest coding.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups

Reporting group title	Placebo

Reporting group description:

Placebo matched to PF-00489791 tablet orally once daily for 12 weeks.

Reporting group title	PF-00489791 20 mg

Reporting group description:

PF-00489791 20 mg tablet orally once daily for 12 weeks.

Serious adverse events	Placebo	PF-00489791 20 mg	
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 64 (9.38%)	13 / 192 (6.77%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Vascular disorders			
Accelerated hypertension			
subjects affected / exposed	0 / 64 (0.00%)	1 / 192 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Prostatectomy			
subjects affected / exposed	1 / 64 (1.56%)	0 / 192 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Chest discomfort			

subjects affected / exposed	0 / 64 (0.00%)	1 / 192 (0.52%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Prostatitis			
subjects affected / exposed	1 / 64 (1.56%)	0 / 192 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 64 (0.00%)	1 / 192 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	0 / 64 (0.00%)	1 / 192 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary oedema			
subjects affected / exposed	0 / 64 (0.00%)	1 / 192 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	1 / 64 (1.56%)	0 / 192 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Injury, poisoning and procedural complications			
Procedural hypotension			
subjects affected / exposed	1 / 64 (1.56%)	0 / 192 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction			

subjects affected / exposed	1 / 64 (1.56%)	0 / 192 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	0 / 64 (0.00%)	1 / 192 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	0 / 64 (0.00%)	2 / 192 (1.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery disease			
subjects affected / exposed	0 / 64 (0.00%)	1 / 192 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	0 / 64 (0.00%)	2 / 192 (1.04%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hemiparesis			
subjects affected / exposed	0 / 64 (0.00%)	1 / 192 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 64 (1.56%)	3 / 192 (1.56%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhagic anaemia			
subjects affected / exposed	0 / 64 (0.00%)	1 / 192 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			

Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 64 (0.00%)	1 / 192 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Melaena			
subjects affected / exposed	0 / 64 (0.00%)	1 / 192 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophagitis			
subjects affected / exposed	0 / 64 (0.00%)	1 / 192 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	0 / 64 (0.00%)	1 / 192 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	0 / 64 (0.00%)	1 / 192 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure acute			
subjects affected / exposed	1 / 64 (1.56%)	1 / 192 (0.52%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Gouty arthritis			
subjects affected / exposed	1 / 64 (1.56%)	0 / 192 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Cellulitis			

subjects affected / exposed	1 / 64 (1.56%)	0 / 192 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Localised infection			
subjects affected / exposed	0 / 64 (0.00%)	1 / 192 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 64 (0.00%)	1 / 192 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hypoglycaemia			
subjects affected / exposed	1 / 64 (1.56%)	0 / 192 (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-00489791 20 mg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	35 / 64 (54.69%)	104 / 192 (54.17%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Monoclonal gammopathy			
subjects affected / exposed	1 / 64 (1.56%)	0 / 192 (0.00%)	
occurrences (all)	1	0	
Vascular disorders			
Aortic aneurysm			
subjects affected / exposed	0 / 64 (0.00%)	1 / 192 (0.52%)	
occurrences (all)	0	1	
Flushing			
subjects affected / exposed	0 / 64 (0.00%)	1 / 192 (0.52%)	
occurrences (all)	0	1	
Hot flush			

subjects affected / exposed	0 / 64 (0.00%)	1 / 192 (0.52%)	
occurrences (all)	0	1	
Hypertension			
subjects affected / exposed	2 / 64 (3.13%)	9 / 192 (4.69%)	
occurrences (all)	2	9	
Hypotension			
subjects affected / exposed	2 / 64 (3.13%)	0 / 192 (0.00%)	
occurrences (all)	2	0	
Orthostatic hypotension			
subjects affected / exposed	0 / 64 (0.00%)	1 / 192 (0.52%)	
occurrences (all)	0	1	
Peripheral venous disease			
subjects affected / exposed	1 / 64 (1.56%)	0 / 192 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Chest discomfort			
subjects affected / exposed	0 / 64 (0.00%)	1 / 192 (0.52%)	
occurrences (all)	0	1	
Face oedema			
subjects affected / exposed	0 / 64 (0.00%)	1 / 192 (0.52%)	
occurrences (all)	0	1	
Chills			
subjects affected / exposed	0 / 64 (0.00%)	1 / 192 (0.52%)	
occurrences (all)	0	1	
Chest pain			
subjects affected / exposed	0 / 64 (0.00%)	2 / 192 (1.04%)	
occurrences (all)	0	3	
Fatigue			
subjects affected / exposed	1 / 64 (1.56%)	2 / 192 (1.04%)	
occurrences (all)	1	2	
Oedema			
subjects affected / exposed	1 / 64 (1.56%)	3 / 192 (1.56%)	
occurrences (all)	1	3	
Feeling hot			

subjects affected / exposed	0 / 64 (0.00%)	1 / 192 (0.52%)	
occurrences (all)	0	1	
Peripheral swelling			
subjects affected / exposed	0 / 64 (0.00%)	2 / 192 (1.04%)	
occurrences (all)	0	2	
Oedema peripheral			
subjects affected / exposed	6 / 64 (9.38%)	10 / 192 (5.21%)	
occurrences (all)	6	12	
Pyrexia			
subjects affected / exposed	0 / 64 (0.00%)	4 / 192 (2.08%)	
occurrences (all)	0	4	
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	0 / 64 (0.00%)	1 / 192 (0.52%)	
occurrences (all)	0	1	
Hypersensitivity			
subjects affected / exposed	0 / 64 (0.00%)	1 / 192 (0.52%)	
occurrences (all)	0	2	
Social circumstances			
Immobile			
subjects affected / exposed	0 / 64 (0.00%)	1 / 192 (0.52%)	
occurrences (all)	0	1	
Reproductive system and breast disorders			
Prostatitis			
subjects affected / exposed	1 / 64 (1.56%)	0 / 192 (0.00%)	
occurrences (all)	2	0	
Spontaneous penile erection			
subjects affected / exposed	0 / 64 (0.00%)	2 / 192 (1.04%)	
occurrences (all)	0	2	
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 64 (0.00%)	1 / 192 (0.52%)	
occurrences (all)	0	1	
Cough			

subjects affected / exposed	1 / 64 (1.56%)	0 / 192 (0.00%)	
occurrences (all)	1	0	
Dyspnoea			
subjects affected / exposed	0 / 64 (0.00%)	1 / 192 (0.52%)	
occurrences (all)	0	1	
Dyspnoea exertional			
subjects affected / exposed	0 / 64 (0.00%)	1 / 192 (0.52%)	
occurrences (all)	0	1	
Epistaxis			
subjects affected / exposed	0 / 64 (0.00%)	1 / 192 (0.52%)	
occurrences (all)	0	1	
Nasal congestion			
subjects affected / exposed	0 / 64 (0.00%)	2 / 192 (1.04%)	
occurrences (all)	0	5	
Sinus congestion			
subjects affected / exposed	0 / 64 (0.00%)	1 / 192 (0.52%)	
occurrences (all)	0	1	
Psychiatric disorders			
Nervousness			
subjects affected / exposed	1 / 64 (1.56%)	0 / 192 (0.00%)	
occurrences (all)	1	0	
Investigations			
Amylase increased			
subjects affected / exposed	1 / 64 (1.56%)	1 / 192 (0.52%)	
occurrences (all)	1	1	
Blood calcium decreased			
subjects affected / exposed	0 / 64 (0.00%)	1 / 192 (0.52%)	
occurrences (all)	0	1	
Blood creatine phosphokinase increased			
subjects affected / exposed	3 / 64 (4.69%)	6 / 192 (3.13%)	
occurrences (all)	3	6	
Blood creatinine increased			
subjects affected / exposed	1 / 64 (1.56%)	1 / 192 (0.52%)	
occurrences (all)	1	2	
Blood glucose abnormal			

subjects affected / exposed	1 / 64 (1.56%)	0 / 192 (0.00%)	
occurrences (all)	1	0	
Blood glucose increased			
subjects affected / exposed	1 / 64 (1.56%)	1 / 192 (0.52%)	
occurrences (all)	1	1	
Blood lactate dehydrogenase increased			
subjects affected / exposed	1 / 64 (1.56%)	0 / 192 (0.00%)	
occurrences (all)	1	0	
Blood potassium increased			
subjects affected / exposed	0 / 64 (0.00%)	3 / 192 (1.56%)	
occurrences (all)	0	3	
Blood pressure abnormal			
subjects affected / exposed	0 / 64 (0.00%)	1 / 192 (0.52%)	
occurrences (all)	0	1	
Blood pressure increased			
subjects affected / exposed	0 / 64 (0.00%)	1 / 192 (0.52%)	
occurrences (all)	0	1	
Blood urea increased			
subjects affected / exposed	0 / 64 (0.00%)	2 / 192 (1.04%)	
occurrences (all)	0	2	
Blood uric acid increased			
subjects affected / exposed	2 / 64 (3.13%)	0 / 192 (0.00%)	
occurrences (all)	3	0	
Electrocardiogram ST segment depression			
subjects affected / exposed	0 / 64 (0.00%)	1 / 192 (0.52%)	
occurrences (all)	0	1	
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 64 (1.56%)	0 / 192 (0.00%)	
occurrences (all)	1	0	
Glycosylated haemoglobin increased			
subjects affected / exposed	0 / 64 (0.00%)	1 / 192 (0.52%)	
occurrences (all)	0	1	
Haemoglobin decreased			

subjects affected / exposed	1 / 64 (1.56%)	0 / 192 (0.00%)	
occurrences (all)	1	0	
International normalised ratio increased			
subjects affected / exposed	0 / 64 (0.00%)	1 / 192 (0.52%)	
occurrences (all)	0	1	
Liver function test normal			
subjects affected / exposed	0 / 64 (0.00%)	1 / 192 (0.52%)	
occurrences (all)	0	1	
Lipase increased			
subjects affected / exposed	0 / 64 (0.00%)	2 / 192 (1.04%)	
occurrences (all)	0	2	
Weight increased			
subjects affected / exposed	0 / 64 (0.00%)	1 / 192 (0.52%)	
occurrences (all)	0	1	
Weight decreased			
subjects affected / exposed	0 / 64 (0.00%)	1 / 192 (0.52%)	
occurrences (all)	0	1	
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	1 / 64 (1.56%)	0 / 192 (0.00%)	
occurrences (all)	1	0	
Fall			
subjects affected / exposed	0 / 64 (0.00%)	1 / 192 (0.52%)	
occurrences (all)	0	1	
Humerus fracture			
subjects affected / exposed	0 / 64 (0.00%)	1 / 192 (0.52%)	
occurrences (all)	0	1	
Laceration			
subjects affected / exposed	0 / 64 (0.00%)	1 / 192 (0.52%)	
occurrences (all)	0	1	
Ligament sprain			
subjects affected / exposed	0 / 64 (0.00%)	1 / 192 (0.52%)	
occurrences (all)	0	1	
Lip injury			

subjects affected / exposed	1 / 64 (1.56%)	0 / 192 (0.00%)	
occurrences (all)	1	0	
Procedural pain			
subjects affected / exposed	1 / 64 (1.56%)	0 / 192 (0.00%)	
occurrences (all)	1	0	
Skin abrasion			
subjects affected / exposed	1 / 64 (1.56%)	1 / 192 (0.52%)	
occurrences (all)	1	1	
Spinal compression fracture			
subjects affected / exposed	0 / 64 (0.00%)	1 / 192 (0.52%)	
occurrences (all)	0	1	
Cardiac disorders			
Cardiac failure			
subjects affected / exposed	1 / 64 (1.56%)	1 / 192 (0.52%)	
occurrences (all)	1	1	
Coronary artery disease			
subjects affected / exposed	1 / 64 (1.56%)	1 / 192 (0.52%)	
occurrences (all)	1	1	
Mitral valve incompetence			
subjects affected / exposed	0 / 64 (0.00%)	1 / 192 (0.52%)	
occurrences (all)	0	1	
Palpitations			
subjects affected / exposed	0 / 64 (0.00%)	2 / 192 (1.04%)	
occurrences (all)	0	2	
Nervous system disorders			
Balance disorder			
subjects affected / exposed	0 / 64 (0.00%)	1 / 192 (0.52%)	
occurrences (all)	0	1	
Diabetic neuropathy			
subjects affected / exposed	0 / 64 (0.00%)	1 / 192 (0.52%)	
occurrences (all)	0	1	
Dizziness			
subjects affected / exposed	1 / 64 (1.56%)	7 / 192 (3.65%)	
occurrences (all)	1	7	
Drooling			

subjects affected / exposed	0 / 64 (0.00%)	1 / 192 (0.52%)	
occurrences (all)	0	1	
Dysarthria			
subjects affected / exposed	0 / 64 (0.00%)	1 / 192 (0.52%)	
occurrences (all)	0	1	
Memory impairment			
subjects affected / exposed	1 / 64 (1.56%)	0 / 192 (0.00%)	
occurrences (all)	1	0	
Headache			
subjects affected / exposed	6 / 64 (9.38%)	12 / 192 (6.25%)	
occurrences (all)	7	13	
Paraesthesia			
subjects affected / exposed	0 / 64 (0.00%)	1 / 192 (0.52%)	
occurrences (all)	0	1	
Restless legs syndrome			
subjects affected / exposed	0 / 64 (0.00%)	1 / 192 (0.52%)	
occurrences (all)	0	1	
Somnolence			
subjects affected / exposed	0 / 64 (0.00%)	2 / 192 (1.04%)	
occurrences (all)	0	2	
Tremor			
subjects affected / exposed	1 / 64 (1.56%)	1 / 192 (0.52%)	
occurrences (all)	1	1	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 64 (0.00%)	4 / 192 (2.08%)	
occurrences (all)	0	4	
Iron deficiency anaemia			
subjects affected / exposed	0 / 64 (0.00%)	2 / 192 (1.04%)	
occurrences (all)	0	2	
Neutrophilia			
subjects affected / exposed	0 / 64 (0.00%)	1 / 192 (0.52%)	
occurrences (all)	0	1	
Ear and labyrinth disorders			
Ear haemorrhage			

subjects affected / exposed	0 / 64 (0.00%)	1 / 192 (0.52%)	
occurrences (all)	0	1	
Eye disorders			
Diabetic retinopathy			
subjects affected / exposed	0 / 64 (0.00%)	1 / 192 (0.52%)	
occurrences (all)	0	1	
Eye irritation			
subjects affected / exposed	0 / 64 (0.00%)	2 / 192 (1.04%)	
occurrences (all)	0	2	
Lacrimation increased			
subjects affected / exposed	0 / 64 (0.00%)	1 / 192 (0.52%)	
occurrences (all)	0	1	
Visual acuity reduced			
subjects affected / exposed	0 / 64 (0.00%)	1 / 192 (0.52%)	
occurrences (all)	0	1	
Visual impairment			
subjects affected / exposed	0 / 64 (0.00%)	2 / 192 (1.04%)	
occurrences (all)	0	2	
Gastrointestinal disorders			
Colitis			
subjects affected / exposed	1 / 64 (1.56%)	0 / 192 (0.00%)	
occurrences (all)	1	0	
Abdominal discomfort			
subjects affected / exposed	1 / 64 (1.56%)	0 / 192 (0.00%)	
occurrences (all)	1	0	
Abdominal distension			
subjects affected / exposed	0 / 64 (0.00%)	1 / 192 (0.52%)	
occurrences (all)	0	1	
Constipation			
subjects affected / exposed	2 / 64 (3.13%)	2 / 192 (1.04%)	
occurrences (all)	2	2	
Dry mouth			
subjects affected / exposed	1 / 64 (1.56%)	0 / 192 (0.00%)	
occurrences (all)	1	0	
Diarrhoea			

subjects affected / exposed	2 / 64 (3.13%)	17 / 192 (8.85%)	
occurrences (all)	2	22	
Dyspepsia			
subjects affected / exposed	1 / 64 (1.56%)	12 / 192 (6.25%)	
occurrences (all)	1	13	
Flatulence			
subjects affected / exposed	0 / 64 (0.00%)	1 / 192 (0.52%)	
occurrences (all)	0	1	
Frequent bowel movements			
subjects affected / exposed	0 / 64 (0.00%)	2 / 192 (1.04%)	
occurrences (all)	0	2	
Gastritis erosive			
subjects affected / exposed	0 / 64 (0.00%)	1 / 192 (0.52%)	
occurrences (all)	0	1	
Gastroduodenitis			
subjects affected / exposed	0 / 64 (0.00%)	1 / 192 (0.52%)	
occurrences (all)	0	1	
Gastritis			
subjects affected / exposed	0 / 64 (0.00%)	3 / 192 (1.56%)	
occurrences (all)	0	3	
Irritable bowel syndrome			
subjects affected / exposed	0 / 64 (0.00%)	1 / 192 (0.52%)	
occurrences (all)	0	1	
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 64 (1.56%)	0 / 192 (0.00%)	
occurrences (all)	1	0	
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 64 (0.00%)	4 / 192 (2.08%)	
occurrences (all)	0	4	
Nausea			
subjects affected / exposed	2 / 64 (3.13%)	4 / 192 (2.08%)	
occurrences (all)	2	4	
Large intestine polyp			
subjects affected / exposed	0 / 64 (0.00%)	1 / 192 (0.52%)	
occurrences (all)	0	1	
Oesophageal ulcer			

subjects affected / exposed	0 / 64 (0.00%)	1 / 192 (0.52%)	
occurrences (all)	0	1	
Vomiting			
subjects affected / exposed	2 / 64 (3.13%)	7 / 192 (3.65%)	
occurrences (all)	2	9	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	0 / 64 (0.00%)	1 / 192 (0.52%)	
occurrences (all)	0	1	
Hyperhidrosis			
subjects affected / exposed	0 / 64 (0.00%)	1 / 192 (0.52%)	
occurrences (all)	0	1	
Dry skin			
subjects affected / exposed	2 / 64 (3.13%)	0 / 192 (0.00%)	
occurrences (all)	2	0	
Neuropathic ulcer			
subjects affected / exposed	0 / 64 (0.00%)	1 / 192 (0.52%)	
occurrences (all)	0	1	
Neurodermatitis			
subjects affected / exposed	0 / 64 (0.00%)	1 / 192 (0.52%)	
occurrences (all)	0	1	
Night sweats			
subjects affected / exposed	0 / 64 (0.00%)	1 / 192 (0.52%)	
occurrences (all)	0	1	
Pruritus			
subjects affected / exposed	0 / 64 (0.00%)	3 / 192 (1.56%)	
occurrences (all)	0	4	
Pruritus generalised			
subjects affected / exposed	0 / 64 (0.00%)	1 / 192 (0.52%)	
occurrences (all)	0	1	
Rash			
subjects affected / exposed	1 / 64 (1.56%)	0 / 192 (0.00%)	
occurrences (all)	1	0	
Rash pruritic			
subjects affected / exposed	0 / 64 (0.00%)	1 / 192 (0.52%)	
occurrences (all)	0	1	

Renal and urinary disorders			
Nocturia			
subjects affected / exposed	1 / 64 (1.56%)	0 / 192 (0.00%)	
occurrences (all)	1	0	
Polyuria			
subjects affected / exposed	1 / 64 (1.56%)	0 / 192 (0.00%)	
occurrences (all)	1	0	
Pollakiuria			
subjects affected / exposed	0 / 64 (0.00%)	2 / 192 (1.04%)	
occurrences (all)	0	2	
Proteinuria			
subjects affected / exposed	0 / 64 (0.00%)	1 / 192 (0.52%)	
occurrences (all)	0	1	
Renal cyst			
subjects affected / exposed	0 / 64 (0.00%)	1 / 192 (0.52%)	
occurrences (all)	0	1	
Renal impairment			
subjects affected / exposed	1 / 64 (1.56%)	0 / 192 (0.00%)	
occurrences (all)	1	0	
Urinary incontinence			
subjects affected / exposed	1 / 64 (1.56%)	0 / 192 (0.00%)	
occurrences (all)	1	0	
Urinary retention			
subjects affected / exposed	0 / 64 (0.00%)	1 / 192 (0.52%)	
occurrences (all)	0	1	
Endocrine disorders			
Autoimmune thyroiditis			
subjects affected / exposed	0 / 64 (0.00%)	1 / 192 (0.52%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 64 (1.56%)	3 / 192 (1.56%)	
occurrences (all)	1	3	
Arthritis			
subjects affected / exposed	0 / 64 (0.00%)	1 / 192 (0.52%)	
occurrences (all)	0	1	

Back pain			
subjects affected / exposed	2 / 64 (3.13%)	5 / 192 (2.60%)	
occurrences (all)	2	7	
Joint swelling			
subjects affected / exposed	0 / 64 (0.00%)	2 / 192 (1.04%)	
occurrences (all)	0	3	
Muscle spasms			
subjects affected / exposed	2 / 64 (3.13%)	1 / 192 (0.52%)	
occurrences (all)	2	1	
Musculoskeletal pain			
subjects affected / exposed	1 / 64 (1.56%)	0 / 192 (0.00%)	
occurrences (all)	1	0	
Neck pain			
subjects affected / exposed	0 / 64 (0.00%)	1 / 192 (0.52%)	
occurrences (all)	0	1	
Myalgia			
subjects affected / exposed	0 / 64 (0.00%)	2 / 192 (1.04%)	
occurrences (all)	0	2	
Osteoarthritis			
subjects affected / exposed	0 / 64 (0.00%)	1 / 192 (0.52%)	
occurrences (all)	0	1	
Pain in extremity			
subjects affected / exposed	0 / 64 (0.00%)	3 / 192 (1.56%)	
occurrences (all)	0	3	
Osteopenia			
subjects affected / exposed	1 / 64 (1.56%)	0 / 192 (0.00%)	
occurrences (all)	1	0	
Spinal osteoarthritis			
subjects affected / exposed	0 / 64 (0.00%)	1 / 192 (0.52%)	
occurrences (all)	0	1	
Infections and infestations			
Abscess limb			
subjects affected / exposed	0 / 64 (0.00%)	1 / 192 (0.52%)	
occurrences (all)	0	1	
Cellulitis			

subjects affected / exposed	0 / 64 (0.00%)	1 / 192 (0.52%)	
occurrences (all)	0	1	
Bronchitis			
subjects affected / exposed	2 / 64 (3.13%)	1 / 192 (0.52%)	
occurrences (all)	2	1	
Eye infection bacterial			
subjects affected / exposed	0 / 64 (0.00%)	1 / 192 (0.52%)	
occurrences (all)	0	1	
Conjunctivitis			
subjects affected / exposed	0 / 64 (0.00%)	1 / 192 (0.52%)	
occurrences (all)	0	1	
Gastroenteritis			
subjects affected / exposed	0 / 64 (0.00%)	1 / 192 (0.52%)	
occurrences (all)	0	1	
Influenza			
subjects affected / exposed	0 / 64 (0.00%)	3 / 192 (1.56%)	
occurrences (all)	0	4	
Lower respiratory tract infection			
subjects affected / exposed	0 / 64 (0.00%)	1 / 192 (0.52%)	
occurrences (all)	0	1	
Laryngitis			
subjects affected / exposed	1 / 64 (1.56%)	0 / 192 (0.00%)	
occurrences (all)	1	0	
Mastitis fungal			
subjects affected / exposed	0 / 64 (0.00%)	1 / 192 (0.52%)	
occurrences (all)	0	1	
Nasopharyngitis			
subjects affected / exposed	1 / 64 (1.56%)	9 / 192 (4.69%)	
occurrences (all)	1	9	
Onychomycosis			
subjects affected / exposed	1 / 64 (1.56%)	0 / 192 (0.00%)	
occurrences (all)	1	0	
Pharyngitis			
subjects affected / exposed	0 / 64 (0.00%)	2 / 192 (1.04%)	
occurrences (all)	0	2	
Pneumonia			

subjects affected / exposed	0 / 64 (0.00%)	1 / 192 (0.52%)	
occurrences (all)	0	1	
Respiratory tract infection			
subjects affected / exposed	0 / 64 (0.00%)	1 / 192 (0.52%)	
occurrences (all)	0	1	
Tooth infection			
subjects affected / exposed	1 / 64 (1.56%)	0 / 192 (0.00%)	
occurrences (all)	1	0	
Rhinitis			
subjects affected / exposed	0 / 64 (0.00%)	1 / 192 (0.52%)	
occurrences (all)	0	1	
Sinusitis			
subjects affected / exposed	0 / 64 (0.00%)	1 / 192 (0.52%)	
occurrences (all)	0	1	
Upper respiratory tract infection			
subjects affected / exposed	1 / 64 (1.56%)	6 / 192 (3.13%)	
occurrences (all)	1	8	
Urinary tract infection			
subjects affected / exposed	1 / 64 (1.56%)	0 / 192 (0.00%)	
occurrences (all)	1	0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 64 (0.00%)	1 / 192 (0.52%)	
occurrences (all)	0	1	
Gout			
subjects affected / exposed	0 / 64 (0.00%)	2 / 192 (1.04%)	
occurrences (all)	0	2	
Hyperamylasaemia			
subjects affected / exposed	1 / 64 (1.56%)	0 / 192 (0.00%)	
occurrences (all)	1	0	
Hyperglycaemia			
subjects affected / exposed	1 / 64 (1.56%)	4 / 192 (2.08%)	
occurrences (all)	1	4	
Hyperuricaemia			
subjects affected / exposed	1 / 64 (1.56%)	3 / 192 (1.56%)	
occurrences (all)	1	3	

Hyperkalaemia			
subjects affected / exposed	1 / 64 (1.56%)	2 / 192 (1.04%)	
occurrences (all)	1	2	
Hypoglycaemia			
subjects affected / exposed	1 / 64 (1.56%)	1 / 192 (0.52%)	
occurrences (all)	1	1	
Vitamin D deficiency			
subjects affected / exposed	0 / 64 (0.00%)	1 / 192 (0.52%)	
occurrences (all)	0	1	
Hyponatraemia			
subjects affected / exposed	1 / 64 (1.56%)	0 / 192 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 May 2011	1)Entry criterion of UACR lowered to 300 milligram per gram (mg/g) in order to allow assessment of the effects of PF-00489791 in the lower part of the macroalbuminuric range. This revised range more fully represented the patient population at risk of disease progression. 2)Blood pressure at entry amended to 150/100 mmHg as this was more reflective of the at-risk patient population and allowed the study population to reflect this. 3)Estimated glomerular filtration rate (eGFR), which takes gender, age and African/Caribbean status into account remained as the determinant of renal function at study entry. Serum creatinine was continued to be monitored in subjects throughout study participation.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported