Clinical trial results:
A Phase 2, Randomized, Double-Masked, Placebo Controlled, Parallel Group, Multi-Center Study to Compare the Efficacy and Safety of a Chemokine CCR2/5 Receptor Antagonist (PF-04634817) With That of Ranibizumab in Adult Subjects With Diabetic Macular Edema

Summary

EudraCT number	2013-003147-27
Trial protocol	HU DE CZ PL
Global end of trial date	11 August 2015

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	B1261009

Additional study identifiers

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

Notes:

Sponsors

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

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	17 February 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	11 August 2015
Global end of trial reached?	Yes
Global end of trial date	11 August 2015
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The main objective was to evaluate whether the clinical efficacy of PF-04634817 is non-inferior to ranibizumab, as measured by change from baseline in best corrected visual acuity after 12 weeks of treatment in subjects with diabetic macular edema (DME).

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	14 November 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Bulgaria: 8
Country: Number of subjects enrolled	Czech Republic: 23
Country: Number of subjects enrolled	Germany: 9
Country: Number of subjects enrolled	Hungary: 20
Country: Number of subjects enrolled	Israel: 22
Country: Number of subjects enrolled	Moldova, Republic of: 21
Country: Number of subjects enrolled	Poland: 1
Country: Number of subjects enrolled	Romania: 7
Country: Number of subjects enrolled	United States: 87
Worldwide total number of subjects	198
EEA total number of subjects	68

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)	121
From 65 to 84 years	76
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

The study was planned to enroll approximately 100 subjects per arm and assumed a dropout rate of approximately 10%.

Pre-assignment

Screening details:

A total of 475 subjects were screened, of which 199 subjects were assigned to study treatment.

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	Investigator, Subject

Arms

Are arms mutually exclusive?	Yes
Arm title	PF-04634817 200 mg QD

Arm description:

Participants received 50 mg tablets of PF-04634817 and masked sham therapy.

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:

Oral PF 04634817 200 mg once daily (QD). Each daily dose was comprised of 4 x 50 mg tablets of PF 04634817.

Arm title	Placebo QD + Ranibizumab 0.3 mg

Arm description:

Participants received Ranibizumab 0.3 mg intravitreal injection and matching placebo.

Arm type	Placebo
Investigational medicinal product name	Ranibizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravitreal use

Dosage and administration details:

Intravitreal administration of ranibizumab 0.3 mg given monthly

Arm title	Placebo QD + Ranibizumab 0.5 mg

Arm description:

Participants received Ranibizumab 0.5 mg intravitreal injection and matching placebo.

Arm type	Placebo

Investigational medicinal product name	Ranibizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravitreal use

Dosage and administration details:

Intravitreal administration of ranibizumab 0.5 mg, given monthly.

Number of subjects in period 1	PF-04634817 200 mg QD	Placebo QD + Ranibizumab 0.3 mg	Placebo QD + Ranibizumab 0.5 mg
Started	99	43	56
Received treatment	99	43	56
Completed	84	36	47
Not completed	15	7	9
Consent withdrawn by subject	6	3	5
Does not meet entrance criteria	1	-	-
Adverse event, non-fatal	4	1	3
Unspecified	1	2	-
Medication error without associated AE	1	-	1
Lost to follow-up	1	1	-
Protocol deviation	1	-	-

Baseline characteristics

Reporting groups	
Reporting group title	PF-04634817 200 mg QD
Reporting group description:	
Participants received 50 mg tablets of PF-04634817 and masked sham therapy.	
Reporting group title	Placebo QD + Ranibizumab 0.3 mg
Reporting group description:	
Participants received Ranibizumab 0.3 mg intravitreal injection and matching placebo.	
Reporting group title	Placebo QD + Ranibizumab 0.5 mg
Reporting group description:	
Participants received Ranibizumab 0.5 mg intravitreal injection and matching placebo.	

Reporting group values	PF-04634817 200 mg QD	Placebo QD + Ranibizumab 0.3 mg	Placebo QD + Ranibizumab 0.5 mg
Number of subjects	99	43	56
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	60	33	28
From 65-84 years	39	10	27
85 years and over	0	0	1
Age Continuous Units: years			
arithmetic mean	62.5	60.4	63.4
standard deviation	± 8.8	± 7.5	± 8.4
Gender, Male/Female Units: Participants			
FEMALE	40	17	18
MALE	59	26	38

Reporting group values	Total		
Number of subjects	198		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	121		

From 65-84 years	76		
85 years and over	1		

Age Continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Gender, Male/Female			
Units: Participants			
FEMALE	75		
MALE	123		

Subject analysis sets

Subject analysis set title	Placebo QD + Ranibizumab 0.3 mg/0.5 mg
Subject analysis set type	Full analysis

Subject analysis set description:

Participants received Ranibizumab 0.3 mg/0.5 mg intravitreal injection and matching placebo.

Reporting group values	Placebo QD + Ranibizumab 0.3 mg/0.5 mg		
Number of subjects	99		
Age categorical			
Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	61		
From 65-84 years	37		
85 years and over	1		
Age Continuous			
Units: years			
arithmetic mean	62.1		
standard deviation	± 8.1		
Gender, Male/Female			
Units: Participants			
FEMALE	35		
MALE	64		

End points

End points reporting groups

Reporting group title	PF-04634817 200 mg QD
Reporting group description:	
Participants received 50 mg tablets of PF-04634817 and masked sham therapy.	
Reporting group title	Placebo QD + Ranibizumab 0.3 mg
Reporting group description:	
Participants received Ranibizumab 0.3 mg intravitreal injection and matching placebo.	
Reporting group title	Placebo QD + Ranibizumab 0.5 mg
Reporting group description:	
Participants received Ranibizumab 0.5 mg intravitreal injection and matching placebo.	
Subject analysis set title	Placebo QD + Ranibizumab 0.3 mg/0.5 mg
Subject analysis set type	Full analysis
Subject analysis set description:	
Participants received Ranibizumab 0.3 mg/0.5 mg intravitreal injection and matching placebo.	

Primary: Mean Letter Change from Baseline at Week 12 in Best Corrected Visual Acuity (BCVA) Compared to Ranibizumab

End point title	Mean Letter Change from Baseline at Week 12 in Best Corrected Visual Acuity (BCVA) Compared to Ranibizumab
End point description:	
Refraction and visual acuity were assessed through the BCVA obtained using the retro illuminated early treatment diabetic retinopathy study (ETDRS) charts. Distance visual acuity was expressed as an ETDRS score (number of letters correctly read).	
End point type	Primary
End point timeframe:	
Baseline (Day 0) and Week 12	

End point values	PF-04634817 200 mg QD	Placebo QD + Ranibizumab 0.3 mg	Placebo QD + Ranibizumab 0.5 mg	Placebo QD + Ranibizumab 0.3 mg/0.5 mg
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	87	38	53	91
Units: Letters				
least squares mean (confidence interval 80%)	1.55 (-2.21 to 5.3)	3.87 (0.09 to 7.65)	4.03 (0.17 to 7.9)	3.96 (0.28 to 7.64)

Statistical analyses

Statistical analysis title	Change From Baseline in BCVA Score
Statistical analysis description:	
The null hypothesis was that the difference, in the mean change from baseline in BCVA in the PF-04634817 group,and the control group is less than or equal to -3 letters.	
Comparison groups	PF-04634817 200 mg QD v Placebo QD + Ranibizumab 0.3 mg

Number of subjects included in analysis	125
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	= 0.1271
Method	Mixed models analysis
Parameter estimate	Difference in LS means
Point estimate	-2.32
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-4.27
upper limit	-0.37
Variability estimate	Standard error of the mean
Dispersion value	1.52

Notes:

[1] - Non inferiority was to be declared if the lower limit of the confidence interval for the mean difference at Week 12 is greater than -3.0 letters.

Statistical analysis title	Change From Baseline in BCVA Score

Statistical analysis description:

The null hypothesis was that the difference, in the mean change from baseline in BCVA in the PF-04634817 group,and the control group is less than or equal to -3 letters.

Comparison groups	PF-04634817 200 mg QD v Placebo QD + Ranibizumab 0.5 mg
Number of subjects included in analysis	140
Analysis specification	Pre-specified
Analysis type	other[2]
P-value	= 0.0699
Method	Mixed models analysis
Parameter estimate	Difference in LS means
Point estimate	-2.48
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-4.24
upper limit	-0.73
Variability estimate	Standard error of the mean
Dispersion value	1.36

Notes:

[2] - Non inferiority was to be declared if the lower limit of the confidence interval for the mean difference at Week 12 is greater than -3.0 letters.

Statistical analysis title	Change From Baseline in BCVA Score

Statistical analysis description:

The null hypothesis was that the difference, in the mean change from baseline in BCVA in the PF-04634817 group,and the control group is less than or equal to -3 letters.

Comparison groups	PF-04634817 200 mg QD v Placebo QD + Ranibizumab 0.3 mg v Placebo QD + Ranibizumab 0.5 mg

Number of subjects included in analysis	178
Analysis specification	Pre-specified
Analysis type	other[3]
P-value	= 0.0399
Method	Mixed models analysis
Parameter estimate	Difference in LS means
Point estimate	-2.41
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-3.91
upper limit	-0.91
Variability estimate	Standard error of the mean
Dispersion value	1.17

Notes:

[3] - Non inferiority was to be declared if the lower limit of the confidence interval for the mean difference at Week 12 is greater than -3.0 letters.

Secondary: Proportion of Subjects Gaining 15 ETDRS Letters in BCVA from Baseline at Week 12

End point title	Proportion of Subjects Gaining 15 ETDRS Letters in BCVA from Baseline at Week 12

End point description:

Refraction and visual acuity were assessed through the BCVA obtained using the retro illuminated ETDRS charts. Distance visual acuity was expressed as an ETDRS score (number of letters correctly read).

End point type	Secondary

End point timeframe:

Baseline (Day 0) and Week 12

End point values	PF-04634817 200 mg QD	Placebo QD + Ranibizumab 0.3 mg	Placebo QD + Ranibizumab 0.5 mg	Placebo QD + Ranibizumab 0.3 mg/0.5 mg
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	87	38	53	91
Units: percentage of participants				
number (not applicable)	0.069	0.2105	0.1132	0.1538

Statistical analyses

Statistical analysis title	Proportion of Subjects Gaining 15 ETDRS Letters
Comparison groups	PF-04634817 200 mg QD v Placebo QD + Ranibizumab 0.3 mg
Number of subjects included in analysis	125
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0218
Method	Barnard test
Parameter estimate	Risk difference (RD)
Point estimate	-0.1416

Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-0.2483
upper limit	-0.0467

Statistical analysis title	Proportion of Subjects Gaining 15 ETDRS Letters
Statistical analysis description: Baseline in BCVA in the PF-04634817 group,and the control group is less than or equal to -3 letters.	
Comparison groups	PF-04634817 200 mg QD v Placebo QD + Ranibizumab 0.5 mg
Number of subjects included in analysis	140
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.4209
Method	Barnard test
Parameter estimate	Risk difference (RD)
Point estimate	-0.0442
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-0.1217
upper limit	0.0261

Statistical analysis title	Proportion of Subjects Gaining 15 ETDRS Letters
Comparison groups	PF-04634817 200 mg QD v Placebo QD + Ranibizumab 0.3 mg v Placebo QD + Ranibizumab 0.5 mg
Number of subjects included in analysis	178
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0778
Method	Barnard test.
Parameter estimate	Risk difference (RD)
Point estimate	-0.0849
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-0.1516
upper limit	-0.0168

Secondary: Mean Change From Baseline in Central Subfield Retinal Thickness in the Study Eye at Week 12

End point title	Mean Change From Baseline in Central Subfield Retinal Thickness in the Study Eye at Week 12

End point description:

A central reading center was used for the evaluation. A photographer or technician pre certified (“study certified”) by the Central Reading Center ought to perform all optical coherence tomography (OCT) imaging. Use of a Spectralis or Cirrus OCT was acceptable.

End point type	Secondary

End point timeframe:

Baseline (Day 0) and Week 12

End point values	PF-04634817 200 mg QD	Placebo QD + Ranibizumab 0.3 mg	Placebo QD + Ranibizumab 0.5 mg	Placebo QD + Ranibizumab 0.3 mg/0.5 mg
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	83	36	43	79
Units: Letters				
least squares mean (confidence interval 80%)	1.73 (-50.41 to 53.87)	-112.35 (-164.5 to -60.23)	-64.09 (-118 to -10.17)	-85.59 (-136.8 to -34.43)

Statistical analyses

Statistical analysis title	Changes in Central Subfield Retinal Thickness
Comparison groups	PF-04634817 200 mg QD v Placebo QD + Ranibizumab 0.3 mg
Number of subjects included in analysis	119
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Difference in LS means
Point estimate	114.07
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	88.56
upper limit	139.59
Variability estimate	Standard error of the mean
Dispersion value	19.84

Statistical analysis title	Changes in Central Subfield Retinal Thickness
Comparison groups	PF-04634817 200 mg QD v Placebo QD + Ranibizumab 0.5 mg
Number of subjects included in analysis	126
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0004
Method	Mixed models analysis
Parameter estimate	Difference in LS means
Point estimate	65.81

Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	42.2
upper limit	89.43
Variability estimate	Standard error of the mean
Dispersion value	18.36

Statistical analysis title	Changes in Central Subfield Retinal Thickness
Comparison groups	PF-04634817 200 mg QD v Placebo QD + Ranibizumab 0.3 mg v Placebo QD + Ranibizumab 0.5 mg
Number of subjects included in analysis	162
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Difference in LS means
Point estimate	87.32
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	67.45
upper limit	107.19
Variability estimate	Standard error of the mean
Dispersion value	15.44

Secondary: Mean Change From Baseline in the Area of Fluorescein Leakage in the Study Eye at Week 12

End point title	Mean Change From Baseline in the Area of Fluorescein Leakage in the Study Eye at Week 12

End point description:

Fluorescein Angiography (FA) using certified digital systems was taken by a photographer who had been pre-certified ("study-certified") by the Central Reading Center. They were evaluated by the Central Reading Center.

End point type	Secondary

End point timeframe:

Baseline (Day 0) and Week 12

End point values	PF-04634817 200 mg QD	Placebo QD + Ranibizumab 0.3 mg	Placebo QD + Ranibizumab 0.5 mg	Placebo QD + Ranibizumab 0.3 mg/0.5 mg
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	86	36	50	86
Units: Letters				
least squares mean (confidence interval 80%)	1.02 (-3.8 to 5.85)	-6.96 (-11.66 to -2.26)	-5.32 (-10.23 to -0.41)	-6.05 (-10.76 to -1.34)

Statistical analyses

Statistical analysis title	Changes in the Area of Fluorescein Leakage
Comparison groups	PF-04634817 200 mg QD v Placebo QD + Ranibizumab 0.3 mg
Number of subjects included in analysis	122
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Difference in LS means
Point estimate	7.98
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	6.13
upper limit	9.83
Variability estimate	Standard error of the mean
Dispersion value	1.44

Statistical analysis title	Changes in the Area of Fluorescein Leakage
Comparison groups	PF-04634817 200 mg QD v Placebo QD + Ranibizumab 0.5 mg
Number of subjects included in analysis	136
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Difference in LS means
Point estimate	6.34
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	4.7
upper limit	7.98
Variability estimate	Standard error of the mean
Dispersion value	1.28

Statistical analysis title	Changes in the Area of Fluorescein Leakage
Comparison groups	PF-04634817 200 mg QD v Placebo QD + Ranibizumab 0.3 mg v Placebo QD + Ranibizumab 0.5 mg

Number of subjects included in analysis	172
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Difference in LS means
Point estimate	7.07
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	5.66
upper limit	8.48
Variability estimate	Standard error of the mean
Dispersion value	1.09

Secondary: Mean Change From Baseline in Steps of Diabetic Retinopathy Step (ETDRS Severity Scale) in the Study Eye at Week 12

End point title	Mean Change From Baseline in Steps of Diabetic Retinopathy Step (ETDRS Severity Scale) in the Study Eye at Week 12

End point description:

Stereo color fundus photographs using certified digital systems were taken by a photographer who had been pre-certified ("study certified") by the Central Reading Center. They were evaluated by the Central Reading Center.

End point type	Secondary

End point timeframe:

Baseline (Day 0) and Week 12

End point values	PF-04634817 200 mg QD	Placebo QD + Ranibizumab 0.3 mg	Placebo QD + Ranibizumab 0.5 mg	Placebo QD + Ranibizumab 0.3 mg/0.5 mg
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	82	36	44	80
Units: Letters				
least squares mean (confidence interval 80%)	0.11 (-0.44 to 0.66)	-0.23 (-0.76 to 0.31)	-0.44 (-1 to 0.12)	-0.35 (-0.89 to 0.19)

Statistical analyses

Statistical analysis title	Change in Steps of Diabetic Retinopathy
Comparison groups	PF-04634817 200 mg QD v Placebo QD + Ranibizumab 0.3 mg

Number of subjects included in analysis	118
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0423
Method	ANCOVA
Parameter estimate	Difference in LS means
Point estimate	0.34
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	0.13
upper limit	0.55
Variability estimate	Standard error of the mean
Dispersion value	0.17

Statistical analysis title	Change in Steps of Diabetic Retinopathy
Comparison groups	PF-04634817 200 mg QD v Placebo QD + Ranibizumab 0.5 mg
Number of subjects included in analysis	126
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0004
Method	ANCOVA
Parameter estimate	Difference in LS means
Point estimate	0.55
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	0.36
upper limit	0.75
Variability estimate	Standard error of the mean
Dispersion value	0.15

Statistical analysis title	Change in Steps of Diabetic Retinopathy
Comparison groups	PF-04634817 200 mg QD v Placebo QD + Ranibizumab 0.3 mg v Placebo QD + Ranibizumab 0.5 mg
Number of subjects included in analysis	162
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0004
Method	ANCOVA
Parameter estimate	Difference in LS means
Point estimate	0.46
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	0.3
upper limit	0.63

Variability estimate	Standard error of the mean
Dispersion value	0.13

Secondary: Plasma concentration of PF-04634817 up to Week 12

End point title	Plasma concentration of PF-04634817 up to Week 12[4]

End point description:

End point type	Secondary

End point timeframe:

Week 0, Week 4, Week 8, and Week 12

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: As per statistical analysis plan, placebo samples were not analyzed for PF 04634817 exposure. Only the plasma exposure of PF 04634817 was evaluated at the prespecified timepoints

End point values	PF-04634817 200 mg QD			
Subject group type	Reporting group			
Number of subjects analysed	96			
Units: nanogram (ng)/milliliter (mL)				
geometric mean (geometric coefficient of variation)				
Week 0, Hour 2 (N = 91)	612.5 (± 61)			
Week 4, Hour 0 (N = 88)	180 (± 81)			
Week 4, Hour 2 (N = 87)	682 (± 61)			
Week 8, Hour 0 (N = 90)	159.9 (± 68)			
Week 8, Hour 2 (N = 89)	752 (± 57)			
Week 12 (N = 86)	285.2 (± 105)			

Statistical analyses

No statistical analyses for this end point

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

End point title	Number of Participants with Treatment-Emergent Adverse Events (AEs) or Serious Adverse Events (SAEs)

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.

End point type	Other pre-specified

End point timeframe:

Week 0 to Week 16

End point values	PF-04634817 200 mg QD	Placebo QD + Ranibizumab 0.3 mg	Placebo QD + Ranibizumab 0.5 mg	Placebo QD + Ranibizumab 0.3 mg/0.5 mg
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	99	43	56	99
Units: participants				
Number of Participants with AEs	53	32	27	59
Number of Participants with SAEs	7	2	3	5

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Number of Participants with Potentially Clinically Important Post-Baseline Vital Signs

End point title	Number of Participants with Potentially Clinically Important Post-Baseline Vital Signs

End point description:

Number of participants who met the categorical summary of post-baseline criteria at any time point, defined as: supine pulse rate <40 beats per minute (bpm) or >120 bpm; supine systolic blood pressure (SBP) ≥30 millimeters of mercury (mmHg) change from baseline in same posture; supine diastolic BP (DBP) ≥20 mmHg change from baseline in same posture; supine SBP <90 mmHg; supine DBP <50 mmHg.

End point type	Other pre-specified

End point timeframe:

Week -5 to Week 16

End point values	PF-04634817 200 mg QD	Placebo QD + Ranibizumab 0.3 mg	Placebo QD + Ranibizumab 0.5 mg	Placebo QD + Ranibizumab 0.3 mg/0.5 mg
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	99	42	55	97
Units: participants				
Absolute Supine SBP <90 mm Hg	1	0	0	0
Increase from Baseline in Supine SBP >=30 mm Hg	3	4	3	7
Increase from Baseline in Supine DBP >=20 mm Hg	2	2	2	4
Decrease from Baseline in Supine SBP >=30 mm Hg	3	0	2	2
Decrease from Baseline in Supine DBP >=20 mm Hg	2	0	0	0

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Number of Participants With Laboratory Abnormalities

End point title	Number of Participants With Laboratory Abnormalities

End point description:

The following laboratory parameters were analyzed for abnormalities at any time point: hematology (hemoglobin, hematocrit, red blood cell count (RBC), white blood cell count (WBC) with differential, and platelet count); blood chemistry (sodium, potassium, chloride, bicarbonate, blood urea nitrogen (BUN), creatinine, albumin, calcium, total, direct and indirect bilirubin, gamma glutamyltransferase (GGT), alanine aminotransferase (ALT), aspartate aminotransferase (AST), lactic dehydrogenase (LDH), alkaline phosphatase, creatine phosphokinase (CPK), uric acid, amylase and lipase); follicle-stimulating hormone (FSH) (Weeks -5 to 0 only, for postmenopausal women who have been amenorrheic for at least 12 consecutive months prior to screening visit).

End point type	Other pre-specified

End point timeframe:

Week -5 to Week 16

End point values	PF-04634817 200 mg QD	Placebo QD + Ranibizumab 0.3 mg	Placebo QD + Ranibizumab 0.5 mg	Placebo QD + Ranibizumab 0.3 mg/0.5 mg
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	99	42	55	97
Units: participants	45	19	21	40

Statistical analyses

No statistical analyses for this end point

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

End point title	Number of Participants With Potentially Clinically Significant Electrocardiogram (ECG) Findings

End point description:

ECG parameters included PR interval, QRS interval, and corrected QT interval using Fridericia's formula (QTcF). Criteria for ECG changes meeting potential clinical concern included: PR interval greater than or equal to (>=)300 milliseconds (msec) or >=25% increase when baseline is greater than (>)200 msec and >=50% increase when baseline is less than or equal to (≤)200 msec; QRS interval >=200 msec or >=25% increase when baseline is greater than (>)200 msec and >=50% increase when baseline is less than or equal to (≤)200 msec; QT interval >=500 msec; and QTcF >=450 msec or >=30 msec increase. The number of participants with potentially clinically significant ECG findings at any visit were reported.

End point type	Other pre-specified

End point timeframe:

Week -5 to Week 16

End point values	PF-04634817 200 mg QD	Placebo QD + Ranibizumab 0.3 mg	Placebo QD + Ranibizumab 0.5 mg	Placebo QD + Ranibizumab 0.3 mg/0.5 mg
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	99	43	56	99
Units: participants				
QTcF Interval 450-<480 msec	13	2	4	6
QTcF Interval 480-<500 msec	1	0	0	0
QRS Interval >=50% increase from baseline	0	1	0	1
QTcF Interval 30-<60 msec increase from baseline	6	2	1	3

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Number of Participants With Changes in the Anterior Segment of the Study Eye at Week 12

End point title	Number of Participants With Changes in the Anterior Segment of the Study Eye at Week 12

End point description:

The anterior biomicroscopy exam was done undilated in order to assess whether there was any anterior segment inflammation caused either by ranibizumab or PF-04634817.

End point type	Other pre-specified

End point timeframe:

Week -5 to Week 16

End point values	PF-04634817 200 mg QD	Placebo QD + Ranibizumab 0.3 mg	Placebo QD + Ranibizumab 0.5 mg	Placebo QD + Ranibizumab 0.3 mg/0.5 mg
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	99	43	56	99
Units: participants				
Improvement of findings in Lids	1	0	0	0
New finding (NF)/worsening of findings in Lids	1	0	0	0
Improvement of findings in conjunctiva palpebrae	0	0	0	1
NF/worsening of findings in conjunctiva palpebrae	0	1	0	0
Improvement of findings in conjunctiva bulbi	2	0	0	0
NF/worsening of findings in conjunctiva bulbi	0	0	0	0
Improvement of findings in sclera	0	0	0	0
NF/worsening of findings in sclera	0	0	0	0
Improvement of findings in cornea	1	0	0	0
NF/worsening of findings in cornea	0	0	0	0
Improvement of findings in anterior chamber	0	0	0	0

NF/worsening of findings in anterior chamber	0	0	0	0
Improvement of findings in iris	0	0	0	0
NF/worsening of findings in iris	0	0	0	0
Improvement of findings in lens	0	0	0	0
NF/worsening of findings in lens	0	0	1	1

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Maximum increase of intraocular pressure (IOP) from Baseline in Study Eye

End point title	Maximum increase of intraocular pressure (IOP) from Baseline in Study Eye

End point description:

IOP was measured using Goldmann applanation tonometry. To maintain consistency, it was recommended that the same examiner ought to measure IOP with the same tonometer at each visit for a given subject. Intraocular pressure ought to be measured in the study eye approximately 30 minutes after intravitreal injection or masked sham therapy (performed by unmasked study team member).

End point type	Other pre-specified

End point timeframe:

Week -5 to Week 16

End point values	PF-04634817 200 mg QD	Placebo QD + Ranibizumab 0.3 mg	Placebo QD + Ranibizumab 0.5 mg	Placebo QD + Ranibizumab 0.3 mg/0.5 mg
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	99	43	56	99
Units: mmHg				
arithmetic mean (standard deviation)	2.5 (± 2.58)	6 (± 4.74)	3 (± 3.32)	4.3 (± 4.24)

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Number of Participants With Change in Ophthalmoscopy Examination Results in Study Eye after Administration of Ranibizumab or Masked Sham Therapy at Week 8

End point title	Number of Participants With Change in Ophthalmoscopy Examination Results in Study Eye after Administration of Ranibizumab or Masked Sham Therapy at Week 8

End point description:

Ophthalmoscopy ought to be performed after pupillary dilation to examine the vitreous body, optic nerve head, macular and peripheral retina. All findings, including the presence or absence of vitreous inflammation, ought to be documented. All post-dose ophthalmoscopy assessments ought to be made immediately following the administration of ranibizumab or masked sham therapy.

End point type	Other pre-specified

End point timeframe:
Week -5 to Week 16

End point values	PF-04634817 200 mg QD	Placebo QD + Ranibizumab 0.3 mg	Placebo QD + Ranibizumab 0.5 mg	Placebo QD + Ranibizumab 0.3 mg/0.5 mg
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	99	43	56	99
Units: participants				
Improvement of findings in vitreous body	0	0	0	0
NF/worsening of findings in vitreous body	0	0	0	0
Improvement of findings in optic nerve head	0	0	0	0
NF/worsening of findings in optic nerve head	0	0	0	0
Improvement of findings in retina macula	0	0	0	0
NF/worsening of findings in retina macula	0	0	0	0
Improvement of findings in retina non-macula	0	0	0	0
NF/worsening of findings in retina non-macula	0	0	0	0

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Baseline to Week 12	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups	
Reporting group title	PF-04634817 200 mg QD
Reporting group description:	
Participants received 50 mg tablets of PF 04634817 and masked sham therapy.	
Reporting group title	Placebo QD + Ranibizumab 0.5 mg
Reporting group description:	
Participants received Ranibizumab 0.5 mg intravitreal injection and matching placebo.	
Reporting group title	Placebo QD + Ranibizumab 0.3 mg
Reporting group description:	
Participants received Ranibizumab 0.3 mg intravitreal injection and matching placebo.	

Serious adverse events	PF-04634817 200 mg QD	Placebo QD + Ranibizumab 0.5 mg	Placebo QD + Ranibizumab 0.3 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 99 (7.07%)	3 / 56 (5.36%)	2 / 43 (4.65%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Head injury			
subjects affected / exposed	2 / 99 (2.02%)	0 / 56 (0.00%)	0 / 43 (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
Rib fracture			
subjects affected / exposed	1 / 99 (1.01%)	0 / 56 (0.00%)	0 / 43 (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
Vascular disorders			
Extremity necrosis			
subjects affected / exposed	0 / 99 (0.00%)	1 / 56 (1.79%)	0 / 43 (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

Cardiac disorders			
Aortic valve stenosis			
subjects affected / exposed	1 / 99 (1.01%)	0 / 56 (0.00%)	0 / 43 (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
Cardiac failure			
subjects affected / exposed	1 / 99 (1.01%)	0 / 56 (0.00%)	0 / 43 (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
Coronary artery disease			
subjects affected / exposed	1 / 99 (1.01%)	0 / 56 (0.00%)	0 / 43 (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			
Ischaemic stroke			
subjects affected / exposed	1 / 99 (1.01%)	0 / 56 (0.00%)	0 / 43 (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
VIIth nerve paralysis			
subjects affected / exposed	0 / 99 (0.00%)	1 / 56 (1.79%)	0 / 43 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Pancreatitis chronic			
subjects affected / exposed	0 / 99 (0.00%)	1 / 56 (1.79%)	0 / 43 (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
Vomiting			
subjects affected / exposed	1 / 99 (1.01%)	0 / 56 (0.00%)	0 / 43 (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
Psychiatric disorders			
Personality disorder			

subjects affected / exposed	0 / 99 (0.00%)	0 / 56 (0.00%)	1 / 43 (2.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Paronychia			
subjects affected / exposed	0 / 99 (0.00%)	1 / 56 (1.79%)	0 / 43 (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
Sepsis			
subjects affected / exposed	1 / 99 (1.01%)	0 / 56 (0.00%)	0 / 43 (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
Metabolism and nutrition disorders			
Diabetic ketoacidosis			
subjects affected / exposed	0 / 99 (0.00%)	1 / 56 (1.79%)	0 / 43 (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
Hyperuricaemia			
subjects affected / exposed	0 / 99 (0.00%)	0 / 56 (0.00%)	1 / 43 (2.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoglycaemia			
subjects affected / exposed	1 / 99 (1.01%)	1 / 56 (1.79%)	0 / 43 (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 200 mg QD	Placebo QD + Ranibizumab 0.5 mg	Placebo QD + Ranibizumab 0.3 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	17 / 99 (17.17%)	7 / 56 (12.50%)	15 / 43 (34.88%)
Investigations			
Intraocular pressure increased			

subjects affected / exposed	0 / 99 (0.00%)	3 / 56 (5.36%)	1 / 43 (2.33%)
occurrences (all)	0	5	1
Nervous system disorders			
Headache			
subjects affected / exposed	3 / 99 (3.03%)	0 / 56 (0.00%)	4 / 43 (9.30%)
occurrences (all)	3	0	4
Eye disorders			
Blepharitis			
subjects affected / exposed	1 / 99 (1.01%)	0 / 56 (0.00%)	3 / 43 (6.98%)
occurrences (all)	1	0	3
Conjunctival haemorrhage			
subjects affected / exposed	5 / 99 (5.05%)	0 / 56 (0.00%)	1 / 43 (2.33%)
occurrences (all)	8	0	1
Diabetic retinal oedema			
subjects affected / exposed	4 / 99 (4.04%)	3 / 56 (5.36%)	7 / 43 (16.28%)
occurrences (all)	5	3	9
Eye irritation			
subjects affected / exposed	6 / 99 (6.06%)	0 / 56 (0.00%)	0 / 43 (0.00%)
occurrences (all)	6	0	0
Retinal haemorrhage			
subjects affected / exposed	0 / 99 (0.00%)	0 / 56 (0.00%)	3 / 43 (6.98%)
occurrences (all)	0	0	4
Vitreous haemorrhage			
subjects affected / exposed	2 / 99 (2.02%)	1 / 56 (1.79%)	3 / 43 (6.98%)
occurrences (all)	2	1	3

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 February 2015	Futility analysis was updated to occur after 50% of planned subjects were available and use conditional power for the futility assessment. Update to interim analysis parameters were made to provide a more robust futility analysis.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported