Clinical trial results:
A PHASE 2A RANDOMIZED, DOUBLE-BLINDED, DOUBLE DUMMY, PLACEBO AND ACTIVE CONTROLLED, TWO-WAY CROSS-OVER, FLARE-ENRICHED MULTI-CENTRE CLINICAL TRIAL TO EXAMINE THE PAIN RELIEF PRODUCED BY 2 WEEKS OF DAILY ORAL ADMINISTRATION OF A FATTY ACID AMIDE HYDROLASE (FAAH) INHIBITOR PF-04457845 IN PATIENTS WITH OSTEOARTHRITIS OF THE KNEE.

Summary

EudraCT number	2009-014734-16
Trial protocol	SE
Global end of trial date	21 June 2010

Results information

Result version number	v1 (current)
This version publication date	23 May 2016
First version publication date	29 July 2015

Trial information

Trial identification

Sponsor protocol code	B0541004

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00981357
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	30 March 2011
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	21 June 2010
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of PF-04457845 (administered once daily [QD]) versus placebo in relieving pain in subjects with osteoarthritis of the knee.
To evaluate the safety and tolerability of PF-04457845 in patients with osteoarthritis.

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	02 November 2009
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	1 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Sweden: 1
Country: Number of subjects enrolled	United States: 59
Country: Number of subjects enrolled	Canada: 14
Worldwide total number of subjects	74
EEA total number of subjects	1

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)	50
From 65 to 84 years	24
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Study was conducted at 5 sites in 3 countries from 2 November 2009 to 21 June 2010.

Pre-assignment

Screening details:

74 of 76 randomised subjects were treated. Subjects had an initial 7 day pain assessment period (PAP) for baseline. Subjects then had 14 day double-blind treatment period (1), followed by a 14 day washout. A repeat PAP was then conducted followed by double-blind treatment period 2.

Period 1

Period 1 title	First Intervention Period (2 Week)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	PF-04457845 then Placebo

Arm description:

PF-04457845 tablet was administered once daily (QD) in the first intervention period and then matching placebo tablet orally QD in the second intervention period. A washout period of 2 weeks was maintained between each intervention period during which matching placebo were given orally QD. Following the washout period, a 1 week repeat PAP was also maintained during which matching placebo were given orally QD along with the rescue medication. Subjects were further followed up for 3 weeks.

Arm type	Experimental
Investigational medicinal product name	PF-04457845
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

PF-04457845 4 milligram (mg) tablet was administered QD for 14 days (First Intervention Period).

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

Dosage and administration details:

Placebo matched to PF-04457845 was administered QD for 14 days (First Intervention Period).

Arm title	Placebo then PF-04457845

Arm description:

Placebo matched to PF-04457845 tablet was administered QD in the first intervention period and then PF-04457845 4 mg tablet orally QD in the second intervention period. A washout period of 2 weeks was maintained between each intervention period during which matching placebo were given orally QD. Following the washout period, a 1 week repeat PAP was also maintained during which matching placebo were given orally QD along with the rescue medication. Subjects were further followed up for 3 weeks.

Arm type	Experimental

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

Dosage and administration details:

Placebo matched to PF-04457845 was administered QD for 14 days (First Intervention Period).

Investigational medicinal product name	PF-04457845
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

PF-04457845 4 mg tablet was administered QD for 14 days (First Intervention Period).

Arm title	Naproxen then Placebo

Arm description:

Naproxen tablet was administered twice daily (BID) in the first intervention period and then matching placebo tablet BID in the second intervention period. A washout period of 2 weeks was maintained between each intervention period during which matching placebo were given orally QD. Following the washout period, a 1 week repeat PAP was also maintained during which matching placebo were given orally QD along with the rescue medication. Subjects were further followed up for 3 weeks.

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

Dosage and administration details:

Naproxen 500 mg tablet was administered BID for 14 days (First Intervention Period).

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

Dosage and administration details:

Placebo matched to Naproxen was administered BID for 14 days (First Intervention Period).

Arm title	Placebo then Naproxen

Arm description:

Placebo matched to Naproxen was administered BID in the first intervention period and then matching placebo tablet BID in the second intervention period. A washout period of 2 weeks was maintained between each intervention period during which matching placebo were given orally QD. Following the washout period, a 1 week repeat PAP was also maintained during which matching placebo were given orally QD along with the rescue medication. Subjects were further followed up for 3 weeks.

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

Dosage and administration details:

Placebo matched to Naproxen was administered BID for 14 days (First Intervention Period).

Investigational medicinal product name	Naproxen
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Naproxen 500 mg tablet was administered BID for 14 days (First Intervention Period).

Number of subjects in period 1	PF-04457845 then Placebo	Placebo then PF-04457845	Naproxen then Placebo
Started	19	19	17
Completed	15	18	17
Not completed	4	1	0
'Protocol Violation '	1	1	-
'Withdrawal by Subject '	3	-	-

Number of subjects in period 1	Placebo then Naproxen
Started	19
Completed	19
Not completed	0
'Protocol Violation '	-
'Withdrawal by Subject '	-

Period 2

Period 2 title	Repeat Pain Assessment Period (1 week)
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	PF-04457845 then Placebo

Arm description:

Following the washout period, a 1 week repeat PAP was also maintained during which matching placebo were given orally QD along with the rescue medication. Subjects were further followed up for 3 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:

Placebo matched to PF-04457845 was administered QD for 7 days (Repeat Pain Assessment Period).

Arm title	Placebo then PF-04457845

Arm description:

Following the washout period, a 1 week repeat PAP was also maintained during which matching placebo were given orally QD along with the rescue medication. Subjects were further followed up for 3 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:

Placebo matched to PF-04457845 was administered QD for 7 days (Repeat Pain Assessment Period).

Arm title	Naproxen then Placebo

Arm description:

Following the washout period, a 1 week repeat PAP was also maintained during which matching placebo were given orally QD along with the rescue medication. Subjects were further followed up for 3 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:

Placebo matched to PF-04457845 was administered QD for 7 days (Repeat Pain Assessment Period).

Arm title	Placebo then Naproxen

Arm description:

Following the washout period, a 1 week repeat PAP was also maintained during which matching placebo were given orally QD along with the rescue medication. Subjects were further followed up for 3 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:

Placebo matched to PF-04457845 was administered QD for 7 days (Repeat Pain Assessment Period).

Number of subjects in period 2	PF-04457845 then Placebo	Placebo then PF-04457845	Naproxen then Placebo
Started	15	18	17
Completed	15	18	17

Number of subjects in period 2	Placebo then Naproxen
Started	19
Completed	19

Baseline characteristics

Reporting groups	
Reporting group title	PF-04457845 then Placebo
Reporting group description:	
PF-04457845 tablet was administered once daily (QD) in the first intervention period and then matching placebo tablet orally QD in the second intervention period. A washout period of 2 weeks was maintained between each intervention period during which matching placebo were given orally QD. Following the washout period, a 1 week repeat PAP was also maintained during which matching placebo were given orally QD along with the rescue medication. Subjects were further followed up for 3 weeks.	
Reporting group title	Placebo then PF-04457845
Reporting group description:	
Placebo matched to PF-04457845 tablet was administered QD in the first intervention period and then PF-04457845 4 mg tablet orally QD in the second intervention period. A washout period of 2 weeks was maintained between each intervention period during which matching placebo were given orally QD. Following the washout period, a 1 week repeat PAP was also maintained during which matching placebo were given orally QD along with the rescue medication. Subjects were further followed up for 3 weeks.	
Reporting group title	Naproxen then Placebo
Reporting group description:	
Naproxen tablet was administered twice daily (BID) in the first intervention period and then matching placebo tablet BID in the second intervention period. A washout period of 2 weeks was maintained between each intervention period during which matching placebo were given orally QD. Following the washout period, a 1 week repeat PAP was also maintained during which matching placebo were given orally QD along with the rescue medication. Subjects were further followed up for 3 weeks.	
Reporting group title	Placebo then Naproxen
Reporting group description:	
Placebo matched to Naproxen was administered BID in the first intervention period and then matching placebo tablet BID in the second intervention period. A washout period of 2 weeks was maintained between each intervention period during which matching placebo were given orally QD. Following the washout period, a 1 week repeat PAP was also maintained during which matching placebo were given orally QD along with the rescue medication. Subjects were further followed up for 3 weeks.	

Reporting group values	PF-04457845 then Placebo	Placebo then PF-04457845	Naproxen then Placebo
Number of subjects	19	19	17
Age categorical Units: Subjects			
Less than (<) 18 years	0	0	0
Between 18 and 44 years	0	0	2
Between 45 and 64 years	12	13	12
Greater than or equal to (>=) 65 years	7	6	3
Gender categorical Units: Subjects			
Female	8	14	8
Male	11	5	9

Reporting group values	Placebo then Naproxen	Total	
Number of subjects	19	74	
Age categorical Units: Subjects			
Less than (<) 18 years	0	0	
Between 18 and 44 years	3	5	
Between 45 and 64 years	8	45	

Greater than or equal to (>=) 65 years	8	24	

Gender categorical Units: Subjects			
Female	13	43	
Male	6	31	

End points reporting groups

Reporting group title	PF-04457845 then Placebo

Reporting group description:

PF-04457845 tablet was administered once daily (QD) in the first intervention period and then matching placebo tablet orally QD in the second intervention period. A washout period of 2 weeks was maintained between each intervention period during which matching placebo were given orally QD. Following the washout period, a 1 week repeat PAP was also maintained during which matching placebo were given orally QD along with the rescue medication. Subjects were further followed up for 3 weeks.

Reporting group title	Placebo then PF-04457845

Reporting group description:

Placebo matched to PF-04457845 tablet was administered QD in the first intervention period and then PF-04457845 4 mg tablet orally QD in the second intervention period. A washout period of 2 weeks was maintained between each intervention period during which matching placebo were given orally QD. Following the washout period, a 1 week repeat PAP was also maintained during which matching placebo were given orally QD along with the rescue medication. Subjects were further followed up for 3 weeks.

Reporting group title	Naproxen then Placebo

Reporting group description:

Naproxen tablet was administered twice daily (BID) in the first intervention period and then matching placebo tablet BID in the second intervention period. A washout period of 2 weeks was maintained between each intervention period during which matching placebo were given orally QD. Following the washout period, a 1 week repeat PAP was also maintained during which matching placebo were given orally QD along with the rescue medication. Subjects were further followed up for 3 weeks.

Reporting group title	Placebo then Naproxen

Reporting group description:

Placebo matched to Naproxen was administered BID in the first intervention period and then matching placebo tablet BID in the second intervention period. A washout period of 2 weeks was maintained between each intervention period during which matching placebo were given orally QD. Following the washout period, a 1 week repeat PAP was also maintained during which matching placebo were given orally QD along with the rescue medication. Subjects were further followed up for 3 weeks.

Reporting group title	PF-04457845 then Placebo

Reporting group description:

Following the washout period, a 1 week repeat PAP was also maintained during which matching placebo were given orally QD along with the rescue medication. Subjects were further followed up for 3 weeks.

Reporting group title	Placebo then PF-04457845

Reporting group description:

Following the washout period, a 1 week repeat PAP was also maintained during which matching placebo were given orally QD along with the rescue medication. Subjects were further followed up for 3 weeks.

Reporting group title	Naproxen then Placebo

Reporting group description:

Following the washout period, a 1 week repeat PAP was also maintained during which matching placebo were given orally QD along with the rescue medication. Subjects were further followed up for 3 weeks.

Reporting group title	Placebo then Naproxen

Reporting group description:

Following the washout period, a 1 week repeat PAP was also maintained during which matching placebo were given orally QD along with the rescue medication. Subjects were further followed up for 3 weeks.

Subject analysis set title	PF-04457845
Subject analysis set type	Full analysis

Subject analysis set description:

PF-04457845 4mg tablet was administered orally QD for 2 weeks in first intervention period.

Subject analysis set title	Naproxen
Subject analysis set type	Full analysis

Subject analysis set description:

Naproxen 500mg tablet was administered orally BID for 2 weeks in first intervention period.

Subject analysis set title	Placebo

Subject analysis set type	Full analysis

Subject analysis set description:

Placebo matched to PF-04457845 or Naproxen was administered orally for 2 weeks in first intervention period QD and BID, respectively.

Primary: Western Ontario and McMaster (WOMAC) Osteoarthritis (OA) Index Pain Subscale Score at End of Treatment

End point title	Western Ontario and McMaster (WOMAC) Osteoarthritis (OA) Index Pain Subscale Score at End of Treatment

End point description:

WOMAC Pain subscale is comprised of 5 questions regarding the amount of pain experienced due to OA in the index joint (knee) in the past 48 hours. The WOMAC Pain subscale is calculated as the mean of the scores from the 5 individual questions, and it may not necessarily be a whole (integer) number. The WOMAC Pain subscale scores for each question range from 0 to 4, giving a possible score range of 0-20, with higher scores indicating higher pain. Full Analysis Set (FAS) included all subjects randomized who received at least 1 dose of study drug.

End point type	Primary

End point timeframe:

End of treatment (Day 14 of both the intervention period)

End point values	PF-04457845	Naproxen	Placebo	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	35[1]	36[2]	68[3]	
Units: Units on a scale				
least squares mean (standard error)	9.09 (± 0.452)	7.92 (± 0.445)	9.05 (± 0.326)	

Notes:

[1] - 'N' (number of subjects analyzed) signifies those subjects who were evaluable for this measure.

[2] - 'N' (number of subjects analyzed) signifies those subjects who were evaluable for this measure.

[3] - 'N' (number of subjects analyzed) signifies those subjects who were evaluable for this measure.

Statistical analyses

Statistical analysis title	WOMAC Pain subscale: PF-04457845 vs Placebo

Statistical analysis description:

A mixed effect analysis of covariance (ANCOVA) model was fitted with random subject effect, period and treatment as fixed effects, utilizing the baseline scores as inter- and intra-subject covariates.

Comparison groups	PF-04457845 v Placebo
Number of subjects included in analysis	103
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Least square (LS) mean difference
Point estimate	0.04
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-0.63
upper limit	0.71
Variability estimate	Standard error of the mean
Dispersion value	0.52

Statistical analysis title	WOMAC Pain subscale: Naproxen vs Placebo

Statistical analysis description:

A mixed effect ANCOVA model was fitted with random subject effect, period and treatment as fixed effects, utilizing the baseline scores as
inter and intra-subject covariates.

Comparison groups	Naproxen v Placebo
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	LS mean difference
Point estimate	-1.13
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-1.79
upper limit	-0.47
Variability estimate	Standard error of the mean
Dispersion value	0.511

Primary: Number of Subjects With Treatment Emergent Adverse Event (AEs) or Serious Adverse Event (SAEs)

End point title	Number of Subjects With Treatment Emergent Adverse Event (AEs) or Serious Adverse Event (SAEs)[4]

End point description:

An AE was any untoward medical occurrence attributed to study drug in a subject who received study drug. AE include both SAE and Non-SAE. An SAE was an AE resulting in any of the following outcomes or deemed significant for any other reason: death; initial or prolonged inpatient hospitalization; life-threatening experience (immediate risk of dying); persistent or significant disability/incapacity; congenital anomaly. Treatment-emergent are events between first dose of study drug and up to 14 days after last dose that were absent before treatment or that worsened relative to pretreatment state. Safety data included all randomized subjects who received at least 1 dose of study medication.

End point type	Primary

End point timeframe:

Baseline up to 14 days after last dose of study drug

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive data was planned to be reported for this endpoint.

End point values	PF-04457845	Naproxen	Placebo	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	37	36	70	
Units: Subjects				
AEs	19	21	36	
SAEs	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Western Ontario and McMaster (WOMAC) Stiffness Domain Score

End point title	Western Ontario and McMaster (WOMAC) Stiffness Domain Score

End point description:

WOMAC Stiffness subscale is comprised of 2 questions regarding the amount of stiffness experienced in the index joint (knee) in the past 48 hours. Stiffness is defined as a sensation of decreased ease in with which the patient moves the index joint. The WOMAC Stiffness subscale is calculated as the mean of the scores from the 2 individual questions, and it may not necessarily be a whole (integer) number. The WOMAC Stiffness subscale scores range from 0 to 4 giving a possible score range of 0-8, with higher scores indicating more stiffness. FAS included all subjects randomized who received at least 1 dose of study drug.

End point type	Secondary

End point timeframe:

End of treatment (Day 14 of both the intervention period)

End point values	PF-04457845	Naproxen	Placebo	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	35[5]	36[6]	69[7]	
Units: Units on a scale				
least squares mean (standard error)	3.87 (± 0.231)	3.26 (± 0.228)	3.85 (± 0.165)	

Notes:

[5] - 'N' (number of subjects analyzed) signifies those subjects who were evaluable for this measure.

[6] - 'N' (number of subjects analyzed) signifies those subjects who were evaluable for this measure.

[7] - 'N' (number of subjects analyzed) signifies those subjects who were evaluable for this measure.

Statistical analyses

Statistical analysis title	WOMAC Stiffness subscale: PF-04457845 vs Placebo

Statistical analysis description:

A mixed effect ANCOVA model was fitted with random subject effect, period and treatment as fixed effects, utilizing the baseline scores as inter and intra-subject covariates.

Comparison groups	PF-04457845 v Placebo
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	L S mean difference
Point estimate	0.03
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-0.31
upper limit	0.37
Variability estimate	Standard error of the mean
Dispersion value	0.264

Statistical analysis title	WOMAC Stiffness subscale: Naproxen vs Placebo

Statistical analysis description:

A mixed effect ANCOVA model was fitted with random subject effect, period and treatment as fixed effects, utilizing the baseline scores as
inter- and intra-subject covariates.

Comparison groups	Naproxen v Placebo
Number of subjects included in analysis	105
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	L S mean difference
Point estimate	-0.59
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-0.93
upper limit	-0.25
Variability estimate	Standard error of the mean
Dispersion value	0.261

Secondary: Western Ontario and McMaster (WOMAC) Physical Function Domain Score

End point title	Western Ontario and McMaster (WOMAC) Physical Function Domain Score

End point description:

WOMAC Physical Function subscale is comprised of 17 questions regarding the degree of difficulty experienced due to arthritis in the index joint (knee) in the past 48 hours. The WOMAC Physical Function subscale refers to the subject's ability to move around and perform usual activities of daily living. The WOMAC Physical Function subscale is calculated as the mean of the scores from the 17 individual questions, and it may not be necessarily a whole (integer) number. The WOMAC Physical Function subscale scores for each question, range from 0 to 4 giving a possible score range of 0-68, with higher scores indicating worse function. FAS included all subjects randomized who received at least 1 dose of study drug.

End point type	Secondary

End point timeframe:

End of treatment (Day 14 of both the intervention period)

End point values	PF-04457845	Naproxen	Placebo	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	35[8]	34[9]	68[10]	
Units: Units on a scale				
least squares mean (standard error)	33.4 (± 1.523)	28.62 (± 1.528)	33.1 (± 1.119)	

Notes:

[8] - 'N' (number of subjects analyzed) signifies those subjects who were evaluable for this measure.

[9] - 'N' (number of subjects analyzed) signifies those subjects who were evaluable for this measure.

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

Statistical analyses

Statistical analysis title	WOMAC Physical Function subscale

Statistical analysis description:

A mixed effect ANCOVA model was fitted with random subject effect, period and treatment as fixed effects, utilizing the baseline scores as inter- and intra-subject covariates.

Comparison groups	PF-04457845 v Placebo
Number of subjects included in analysis	103
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	L S mean difference
Point estimate	0.3
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-1.8
upper limit	2.4
Variability estimate	Standard error of the mean
Dispersion value	1.628

Statistical analysis title	WOMAC Physical Function subscale

Statistical analysis description:

A mixed effect ANCOVA model was fitted with random subject effect, period and treatment as fixed effects, utilizing the baseline scores as
inter- and intra-subject covariates.

Comparison groups	Naproxen v Placebo
Number of subjects included in analysis	102
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	L S mean difference
Point estimate	-4.49
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-6.56
upper limit	-2.41
Variability estimate	Standard error of the mean
Dispersion value	1.604

Secondary: Western Ontario and McMaster (WOMAC) Total Score

End point title	Western Ontario and McMaster (WOMAC) Total Score

End point description:

WOMAC Total score was calculated as the sum of all 24 individual questions including sum of the first 5 questions of the WOMAC index (WOMAC pain score) assessing pain with a score range of 0-4, giving a range of 0-20; sum of questions 6 and 7 of the WOMAC index (WOMAC stiffness score) assessing stiffness giving a range from 0-8; and sum of questions 8-24 of the WOMAC index (WOMAC physical function score) assessing physical function with a score range of 0-68 the subjects experienced due to OA in the knee in the past 48 hours. The WOMAC Total score ranges from 0-96, with higher scores indicating more pain, stiffness, and/or worsening of function. FAS included all subjects randomized who received at least 1 dose of study drug.

End point type	Secondary

End point timeframe:

End of treatment (Day 14 of both the intervention period)

End point values	PF-04457845	Naproxen	Placebo	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	35[11]	34[12]	68[13]	
Units: Units on a scale				
least squares mean (standard error)	46.59 (± 2.116)	39.91 (± 2.127)	46.07 (± 1.56)	

Notes:

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

[12] - 'N' (number of subjects analyzed) signifies those subjects who were evaluable for this measure.

[13] - 'N' (number of subjects analyzed) signifies those subjects who were evaluable for this measure.

Statistical analyses

Statistical analysis title	WOMAC Total score: PF-04457845 vs Placebo

Statistical analysis description:

A mixed effect ANCOVA model was fitted with random subject effect, period and treatment as fixed effects, utilizing the baseline scores as inter- and intra-subject covariates.

Comparison groups	PF-04457845 v Placebo
Number of subjects included in analysis	103
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	L S mean difference
Point estimate	0.52
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-2.4
upper limit	3.44
Variability estimate	Standard error of the mean
Dispersion value	2.259

Statistical analysis title	WOMAC Total score: Naproxen vs Placebo

Statistical analysis description:

A mixed effect ANCOVA model was fitted with random subject effect, period and treatment as fixed effects, utilizing the baseline scores as
inter- and intra-subject covariates.

Comparison groups	Naproxen v Placebo
Number of subjects included in analysis	102
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	L S mean difference
Point estimate	-6.15

Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-9.04
upper limit	-3.27
Variability estimate	Standard error of the mean
Dispersion value	2.231

Secondary: Importance Weighted Total Western Ontario and McMaster (WOMAC) Score

End point title	Importance Weighted Total Western Ontario and McMaster (WOMAC) Score

End point description:

Importance Weighted WOMAC Total score was calculated as the WOMAC Total score using all subscales including Pain, Stiffness and Physical Function subscales (24 questions in total,score range: 0=none to 4= extreme,giving a possible overall score range of 0-96) with higher scores indicating more pain, stiffness, and/or worsening of function. Different weights are given according to the importance of each category which was Pain = 42 percentage (%), Stiffness = 21%, and Physical Function = 37%. FAS included all subjects randomized who received at least 1 dose of study drug.

End point type	Secondary

End point timeframe:

End of treatment (Day 14 of both the intervention period)

End point values	PF-04457845	Naproxen	Placebo	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	35[14]	34[15]	68[16]	
Units: Units on a scale				
least squares mean (standard error)	47.78 (± 2.245)	41.15 (± 2.263)	47.31 (± 1.652)	

Notes:

[14] - 'N' (number of subjects analyzed) signifies those subjects who were evaluable for this measure.

[15] - 'N' (number of subjects analyzed) signifies those subjects who were evaluable for this measure.

[16] - 'N' (number of subjects analyzed) signifies those subjects who were evaluable for this measure.

Statistical analyses

Statistical analysis title	PF-04457845 vs Placebo

Statistical analysis description:

Importance Weighted WOMAC Total score: A mixed effect ANCOVA model was fitted with random subject effect, period and treatment as fixed effects, utilizing the baseline scores as inter- and intra-subject covariates.

Comparison groups	PF-04457845 v Placebo
Number of subjects included in analysis	103
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	L S mean difference
Point estimate	0.48

Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-2.65
upper limit	3.61
Variability estimate	Standard error of the mean
Dispersion value	2.424

Statistical analysis title	Naproxen vs Placebo

Statistical analysis description:

Importance Weighted WOMAC Total score: A mixed effect ANCOVA model was fitted with random subject effect, period and treatment as fixed effects, utilizing the baseline scores as inter- and intra-subject covariates.

Comparison groups	Naproxen v Placebo
Number of subjects included in analysis	102
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	L S mean difference
Point estimate	-6.16
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-9.27
upper limit	-3.05
Variability estimate	Standard error of the mean
Dispersion value	2.408

Secondary: Number of Subjects With Rescue Medication Usuage

End point title	Number of Subjects With Rescue Medication Usuage

End point description:

Rescue medication use was collected daily in a daily diary, in which subjects noted the amount of rescue medication (number of pills) taken each day. Subjects were provided with rescue medication paracetamol/acetaminophen throughout the study including the Washout Period and the Initial Pain Assessment Period. Paracetamol/acetaminophen was taken as needed to a maximum of 8 caplets per day or maximum of 4000 mg per day, but must be discontinued 48 hours prior to the Baseline (Day 1). From day 1 onwards, subjects might take up to 4000 mg of acetaminophen per day up to 3 days per week. FAS included all subjects randomized who received at least 1 dose of study drug.

End point type	Secondary

End point timeframe:

Day 7 up to Day 49

End point values	PF-04457845	Naproxen	Placebo	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	37	36	70	
Units: Subjects	22	14	41	

Statistical analyses

No statistical analyses for this end point

Secondary: Average Daily Pain Score During Week 1, 2

End point title	Average Daily Pain Score During Week 1, 2

End point description:

Daily pain scale in subjects recorded their daily pain level during the past 24 hours, using an 11-point numeric rating scale (NRS) subjects would record a daily pain score in their diary (0 was no pain and 10 was worst pain possible). Average of daily score for each week was reported. FAS included all subjects randomized who received at least 1 dose of study drug.

End point type	Secondary

End point timeframe:

Week 1, week 2

End point values	PF-04457845	Naproxen	Placebo	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	37	36	70	
Units: Units on a scale				
least squares mean (standard error)				
Week 1	5.36 (± 0.178)	4.88 (± 0.181)	5.59 (± 0.129)	
Week 2	5.19 (± 0.208)	4.49 (± 0.212)	5.38 (± 0.157)	

Statistical analyses

Statistical analysis title	Week 1: PF-04457845 vs Placebo

Statistical analysis description:

A mixed effect ANCOVA model was fitted with random subject effect, period and treatment as fixed effects, utilizing the baseline average daily pain scores at week 1 as inter- and intra-subject covariates.

Comparison groups	PF-04457845 v Placebo
Number of subjects included in analysis	107
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	L S mean difference
Point estimate	-0.23

Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-0.51
upper limit	0.04
Variability estimate	Standard error of the mean
Dispersion value	0.215

Statistical analysis title	Week 1: Naproxen vs Placebo

Statistical analysis description:

A mixed effect ANCOVA model was fitted with random subject effect, period and treatment as fixed effects, utilizing the baseline average daily pain scores at week 1 as inter- and intra-subject covariates.

Comparison groups	Naproxen v Placebo
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	L S mean difference
Point estimate	-0.71
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-0.99
upper limit	-0.43
Variability estimate	Standard error of the mean
Dispersion value	0.217

Statistical analysis title	Week 2: PF-04457845 vs Placebo

Statistical analysis description:

A mixed effect ANCOVA model was fitted with random subject effect, period and treatment as fixed effects, utilizing the baseline average daily pain scores at week 2 as inter- and intra-subject covariates.

Comparison groups	PF-04457845 v Placebo
Number of subjects included in analysis	107
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	L S mean difference
Point estimate	-0.19
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-0.48
upper limit	0.1
Variability estimate	Standard error of the mean
Dispersion value	0.226

Statistical analysis title	Week 2: Naproxen vs Placebo

Statistical analysis description:

A mixed effect ANCOVA model was fitted with random subject effect, period and treatment as fixed effects, utilizing the baseline average
daily pain scores at week 2 as inter- and intra-subject covariates.

Comparison groups	Naproxen v Placebo
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	L S mean difference
Point estimate	-0.89
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-1.18
upper limit	-0.6
Variability estimate	Standard error of the mean
Dispersion value	0.225

Secondary: Plasma Concentration of PF-04457845

End point title	Plasma Concentration of PF-04457845

End point description:

Plasma concentration for only PF-04457845 arm group has been reported. Plasma concentrations have been calculated by setting concentration values below the lower limit of quantification to zero. The lower limit of quantification is 0.100 nanaogram per millilitre (ng/mL). All subjects who received 1 dose of study drug. 'n' signifies those subjects who were evaluable for this measure at given time points for each group, respectively. 99999 here indicates arithmetic mean and standard deviation as it was not analysed since, no subject was observed above lower limit of quantification.

End point type	Secondary

End point timeframe:

Predose, at 1, 2, 4 hours postdose at Day 1, predose at Day 8, 2 hours post dose at Day 14 post dose any time on Day 22, Day 36

End point values	PF-04457845			
Subject group type	Subject analysis set			
Number of subjects analysed	37			
Units: ng/mL				
arithmetic mean (standard deviation)				
Predose Day 1 (n= 37)	99999 (± 99999)			
1 hour post dose Day 1 (n= 37)	25.25 (± 15.118)			
2 hours post dose Day 1 (n= 37)	20.52 (± 8.2022)			
4 hours post dose Day 1 (n= 37)	17.6 (± 6.2973)			
Pre dose Day 8 (n= 18)	13.58 (± 5.3083)			
2 hours post dose Day 14 (n= 35)	37.13 (± 12.598)			

Post dose Day 22 (n= 17) Post dose Day 36 (n= 18)	0.7299 (± 1.0448) 99999 (± 99999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Residual Fatty Acid Amide Hydrolase (FAAH) Activity in Leucocytes

End point title	Residual Fatty Acid Amide Hydrolase (FAAH) Activity in Leucocytes

End point description:

FAS included all subjects randomized who received at least 1 dose of study drug.

End point type	Secondary

End point timeframe:

Predose at Day 1, Day 36, 2 hours post dose at Day 14, Day 49

End point values	PF-04457845	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	35[17]	33[18]		
Units: nanoMole (nM)				
least squares mean (standard error)	3.45 (± 0.1)	6.75 (± 0.103)		

Notes:

[17] - 'N' (number of subjects analyzed) signifies those subjects who were evaluable for this measure.

[18] - 'N' (number of subjects analyzed) signifies those subjects who were evaluable for this measure.

Statistical analyses

Statistical analysis title	FAAH activity: PF-04457845 vs Placebo

Statistical analysis description:

A mixed effect ANCOVA model was fitted with LS mean adjusted for period and treatment as fixed effects, subjects as a random effect and baseline FAAH scores as covariates (inter and intra subject). The analysis is on the log transformed data; the end of treatment adjusted means, difference and standard error are on the log scale, but the Contrast of Treatments difference and confidence interval have been back transformed for presentation.

Comparison groups	Placebo v PF-04457845
Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Back Transformed Difference
Point estimate	0.04
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	0.0304
upper limit	0.0442

Variability estimate	Standard error of the mean
Dispersion value	0.144

Secondary: Plasma Fatty Acid Amide Levels

End point title	Plasma Fatty Acid Amide Levels

End point description:

Plasma fatty acid amide levels including 9(Z) octadecenamide (OEA), N-palmitoyl ethanolamine (PEA), N-linoleoyl ethanolamide (LEA) and N-arachidonyl ethanolamine (AEA) was estimated from blood plasma samples. FAS included all subjects randomized who have received at least 1 dose of study drug.

End point type	Secondary

End point timeframe:

Predose, at 1, 2 and 4 hours post dose at Day 1, predose at Day 8, 2 hours post dose at Day 14, Day 22, Day 36

End point values	PF-04457845	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	35[19]	33[20]		
Units: ng/mL				
least squares mean (standard error)				
OEA	1.87 (± 0.047)	-0.32 (± 0.049)		
PEA	1.24 (± 0.03)	0.02 (± 0.031)		
LEA	2.02 (± 0.068)	-0.58 (± 0.07)		
AEA	1.19 (± 0.055)	-1.29 (± 0.056)		

Notes:

[19] - 'N' (number of subjects analyzed) signifies those subjects who were evaluable for this measure.

[20] - 'N' (number of subjects analyzed) signifies those subjects who were evaluable for this measure.

Statistical analyses

Statistical analysis title	OEA: PF-04457845 vs Placebo

Statistical analysis description:

A mixed effect ANCOVA model was fitted with LS mean adjusted for period and treatment as fixed effects, subjects as a random effect and baseline OEA as covariates (inter and intra subject). The analysis is on the log transformed data; the end of treatment adjusted means, difference and standard error are on the log scale, but the Contrast of Treatments difference and confidence interval have been back transformed for presentation.

Comparison groups	PF-04457845 v Placebo
Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Back Transformed Difference
Point estimate	8.93
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	8.27
upper limit	9.64

Variability estimate	Standard error of the mean
Dispersion value	0.058

Statistical analysis title	PEA: PF-04457845 vs Placebo

Statistical analysis description:

A mixed effect ANCOVA model was fitted with LS mean adjusted for period and treatment as fixed effects, subjects as a random effect and baseline PEA as covariates (inter and intra subjects). The analysis is on the log transformed data; the end of treatment adjusted means, difference and standard error are on the log scale, but the Contrast of Treatments difference and confidence interval have been back transformed for presentation.

Comparison groups	PF-04457845 v Placebo
Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Back Transformed Difference
Point estimate	3.38
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	3.19
upper limit	3.57
Variability estimate	Standard error of the mean
Dispersion value	0.043

Statistical analysis title	LEA: PF-04457845 vs Placebo

Statistical analysis description:

A mixed effect ANCOVA model was fitted with LS mean adjusted for period and treatment as fixed effects, subjects as a random effect and baseline LEA as covariates (inter and intra subjects). The analysis is on the log transformed data; the end of treatment adjusted means, difference and standard error are on the log scale, but the Contrast of Treatments difference and confidence interval have been back transformed for presentation.

Comparison groups	PF-04457845 v Placebo
Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Back Transformed Difference
Point estimate	13.45
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	11.86
upper limit	15.26
Variability estimate	Standard error of the mean
Dispersion value	0.097

Statistical analysis title	AEA: PF-04457845 vs Placebo

Statistical analysis description:

A mixed effect ANCOVA model was fitted with LS mean adjusted for period and treatment as fixed effects, subjects as a random effect and baseline AEA as covariates (inter and intra subjects). The analysis is on the log transformed data; the end of treatment adjusted means, difference and standard error are on the log scale, but the Contrast of Treatments difference and confidence interval have been back transformed for presentation.

Comparison groups	PF-04457845 v Placebo
Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Back Transformed Difference
Point estimate	11.99
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	11.12
upper limit	12.94
Variability estimate	Standard error of the mean
Dispersion value	0.058

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Baseline up to 14 days after last dose of study drug	
Adverse event reporting additional description:	
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	PF-04457845
Reporting group description:	
PF-04457845 4mg tablet was administered oralyl QD for 2 weeks in first intervention period.	
Reporting group title	NAPROXEN
Reporting group description:	
Naproxen 500mg tablet was administered orally BID for 2 weeks in first intervention period.	
Reporting group title	PLACEBO
Reporting group description:	
Placebo matched to PF-04457845 or Naproxen was administered orally for 2 weeks in first intervention period QD and BID, respectively.	

Serious adverse events	PF-04457845	NAPROXEN	PLACEBO
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 37 (0.00%)	0 / 36 (0.00%)	0 / 70 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

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

Non-serious adverse events	PF-04457845	NAPROXEN	PLACEBO
Total subjects affected by non-serious adverse events			
subjects affected / exposed	19 / 37 (51.35%)	21 / 36 (58.33%)	36 / 70 (51.43%)
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 37 (2.70%)	0 / 36 (0.00%)	0 / 70 (0.00%)
occurrences (all)	1	0	0
General disorders and administration site conditions			

Chills			
subjects affected / exposed	0 / 37 (0.00%)	1 / 36 (2.78%)	0 / 70 (0.00%)
occurrences (all)	0	1	0
Oedema peripheral			
subjects affected / exposed	0 / 37 (0.00%)	1 / 36 (2.78%)	0 / 70 (0.00%)
occurrences (all)	0	1	0
Fatigue			
subjects affected / exposed	0 / 37 (0.00%)	1 / 36 (2.78%)	4 / 70 (5.71%)
occurrences (all)	0	1	4
Pain			
subjects affected / exposed	1 / 37 (2.70%)	0 / 36 (0.00%)	0 / 70 (0.00%)
occurrences (all)	1	0	0
Pyrexia			
subjects affected / exposed	0 / 37 (0.00%)	1 / 36 (2.78%)	0 / 70 (0.00%)
occurrences (all)	0	1	0
Vessel puncture site bruise			
subjects affected / exposed	0 / 37 (0.00%)	1 / 36 (2.78%)	0 / 70 (0.00%)
occurrences (all)	0	1	0
Vessel puncture site pain			
subjects affected / exposed	0 / 37 (0.00%)	1 / 36 (2.78%)	0 / 70 (0.00%)
occurrences (all)	0	1	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 37 (0.00%)	1 / 36 (2.78%)	2 / 70 (2.86%)
occurrences (all)	0	1	2
Epistaxis			
subjects affected / exposed	0 / 37 (0.00%)	0 / 36 (0.00%)	1 / 70 (1.43%)
occurrences (all)	0	0	1
Nasal congestion			
subjects affected / exposed	0 / 37 (0.00%)	0 / 36 (0.00%)	1 / 70 (1.43%)
occurrences (all)	0	0	1
Oropharyngeal pain			
subjects affected / exposed	0 / 37 (0.00%)	0 / 36 (0.00%)	1 / 70 (1.43%)
occurrences (all)	0	0	1
Rhinorrhoea			

subjects affected / exposed	1 / 37 (2.70%)	0 / 36 (0.00%)	1 / 70 (1.43%)
occurrences (all)	1	0	1
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 37 (2.70%)	0 / 36 (0.00%)	0 / 70 (0.00%)
occurrences (all)	1	0	0
Insomnia			
subjects affected / exposed	1 / 37 (2.70%)	1 / 36 (2.78%)	1 / 70 (1.43%)
occurrences (all)	1	1	1
Nightmare			
subjects affected / exposed	0 / 37 (0.00%)	0 / 36 (0.00%)	1 / 70 (1.43%)
occurrences (all)	0	0	1
Investigations			
Blood pressure increased			
subjects affected / exposed	0 / 37 (0.00%)	1 / 36 (2.78%)	0 / 70 (0.00%)
occurrences (all)	0	1	0
Injury, poisoning and procedural complications			
Burns second degree			
subjects affected / exposed	0 / 37 (0.00%)	0 / 36 (0.00%)	1 / 70 (1.43%)
occurrences (all)	0	0	1
Contusion			
subjects affected / exposed	0 / 37 (0.00%)	1 / 36 (2.78%)	0 / 70 (0.00%)
occurrences (all)	0	1	0
Hand fracture			
subjects affected / exposed	1 / 37 (2.70%)	0 / 36 (0.00%)	0 / 70 (0.00%)
occurrences (all)	1	0	0
Lower limb fracture			
subjects affected / exposed	0 / 37 (0.00%)	1 / 36 (2.78%)	0 / 70 (0.00%)
occurrences (all)	0	1	0
Muscle strain			
subjects affected / exposed	1 / 37 (2.70%)	0 / 36 (0.00%)	0 / 70 (0.00%)
occurrences (all)	1	0	0
Tooth fracture			
subjects affected / exposed	0 / 37 (0.00%)	1 / 36 (2.78%)	0 / 70 (0.00%)
occurrences (all)	0	1	0
Nervous system disorders			

Dizziness			
subjects affected / exposed	2 / 37 (5.41%)	2 / 36 (5.56%)	1 / 70 (1.43%)
occurrences (all)	3	4	1
Headache			
subjects affected / exposed	1 / 37 (2.70%)	2 / 36 (5.56%)	10 / 70 (14.29%)
occurrences (all)	3	3	12
Hypoaesthesia			
subjects affected / exposed	0 / 37 (0.00%)	1 / 36 (2.78%)	0 / 70 (0.00%)
occurrences (all)	0	1	0
Paraesthesia			
subjects affected / exposed	0 / 37 (0.00%)	1 / 36 (2.78%)	0 / 70 (0.00%)
occurrences (all)	0	1	0
Presyncope			
subjects affected / exposed	0 / 37 (0.00%)	0 / 36 (0.00%)	1 / 70 (1.43%)
occurrences (all)	0	0	1
Sciatica			
subjects affected / exposed	0 / 37 (0.00%)	0 / 36 (0.00%)	1 / 70 (1.43%)
occurrences (all)	0	0	1
Somnolence			
subjects affected / exposed	1 / 37 (2.70%)	0 / 36 (0.00%)	0 / 70 (0.00%)
occurrences (all)	1	0	0
Speech disorder			
subjects affected / exposed	0 / 37 (0.00%)	0 / 36 (0.00%)	1 / 70 (1.43%)
occurrences (all)	0	0	1
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	0 / 37 (0.00%)	1 / 36 (2.78%)	0 / 70 (0.00%)
occurrences (all)	0	1	0
Vertigo			
subjects affected / exposed	0 / 37 (0.00%)	1 / 36 (2.78%)	0 / 70 (0.00%)
occurrences (all)	0	2	0
Eye disorders			
Dry eye			
subjects affected / exposed	0 / 37 (0.00%)	0 / 36 (0.00%)	1 / 70 (1.43%)
occurrences (all)	0	0	1
Ocular discomfort			

subjects affected / exposed	0 / 37 (0.00%)	1 / 36 (2.78%)	1 / 70 (1.43%)
occurrences (all)	0	1	1
Photopsia			
subjects affected / exposed	0 / 37 (0.00%)	0 / 36 (0.00%)	1 / 70 (1.43%)
occurrences (all)	0	0	1
Vision blurred			
subjects affected / exposed	0 / 37 (0.00%)	0 / 36 (0.00%)	2 / 70 (2.86%)
occurrences (all)	0	0	3
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 37 (0.00%)	0 / 36 (0.00%)	3 / 70 (4.29%)
occurrences (all)	0	0	3
Abdominal distension			
subjects affected / exposed	1 / 37 (2.70%)	0 / 36 (0.00%)	0 / 70 (0.00%)
occurrences (all)	1	0	0
Abdominal pain upper			
subjects affected / exposed	0 / 37 (0.00%)	0 / 36 (0.00%)	1 / 70 (1.43%)
occurrences (all)	0	0	1
Constipation			
subjects affected / exposed	1 / 37 (2.70%)	3 / 36 (8.33%)	0 / 70 (0.00%)
occurrences (all)	1	3	0
Diarrhoea			
subjects affected / exposed	1 / 37 (2.70%)	2 / 36 (5.56%)	3 / 70 (4.29%)
occurrences (all)	1	2	4
Dyspepsia			
subjects affected / exposed	0 / 37 (0.00%)	3 / 36 (8.33%)	0 / 70 (0.00%)
occurrences (all)	0	3	0
Frequent bowel movements			
subjects affected / exposed	0 / 37 (0.00%)	0 / 36 (0.00%)	1 / 70 (1.43%)
occurrences (all)	0	0	1
Gastritis			
subjects affected / exposed	1 / 37 (2.70%)	1 / 36 (2.78%)	0 / 70 (0.00%)
occurrences (all)	1	1	0
Nausea			
subjects affected / exposed	0 / 37 (0.00%)	1 / 36 (2.78%)	2 / 70 (2.86%)
occurrences (all)	0	2	2

Toothache			
subjects affected / exposed	0 / 37 (0.00%)	1 / 36 (2.78%)	0 / 70 (0.00%)
occurrences (all)	0	1	0
Skin and subcutaneous tissue disorders			
Ecchymosis			
subjects affected / exposed	0 / 37 (0.00%)	0 / 36 (0.00%)	1 / 70 (1.43%)
occurrences (all)	0	0	1
Hyperhidrosis			
subjects affected / exposed	0 / 37 (0.00%)	1 / 36 (2.78%)	0 / 70 (0.00%)
occurrences (all)	0	1	0
Night sweats			
subjects affected / exposed	0 / 37 (0.00%)	0 / 36 (0.00%)	1 / 70 (1.43%)
occurrences (all)	0	0	1
Rash			
subjects affected / exposed	0 / 37 (0.00%)	0 / 36 (0.00%)	1 / 70 (1.43%)
occurrences (all)	0	0	1
Renal and urinary disorders			
Pollakiuria			
subjects affected / exposed	0 / 37 (0.00%)	1 / 36 (2.78%)	1 / 70 (1.43%)
occurrences (all)	0	1	1
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 37 (0.00%)	1 / 36 (2.78%)	0 / 70 (0.00%)
occurrences (all)	0	1	0
Back pain			
subjects affected / exposed	2 / 37 (5.41%)	2 / 36 (5.56%)	2 / 70 (2.86%)
occurrences (all)	2	2	2
Bursitis			
subjects affected / exposed	0 / 37 (0.00%)	1 / 36 (2.78%)	0 / 70 (0.00%)
occurrences (all)	0	2	0
Chondritis			
subjects affected / exposed	1 / 37 (2.70%)	0 / 36 (0.00%)	0 / 70 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal pain			
subjects affected / exposed	0 / 37 (0.00%)	1 / 36 (2.78%)	0 / 70 (0.00%)
occurrences (all)	0	1	0

Myalgia			
subjects affected / exposed	0 / 37 (0.00%)	1 / 36 (2.78%)	0 / 70 (0.00%)
occurrences (all)	0	1	0
Osteoarthritis			
subjects affected / exposed	0 / 37 (0.00%)	1 / 36 (2.78%)	0 / 70 (0.00%)
occurrences (all)	0	1	0
Pain in extremity			
subjects affected / exposed	0 / 37 (0.00%)	1 / 36 (2.78%)	1 / 70 (1.43%)
occurrences (all)	0	1	1
Infections and infestations			
Ear infection			
subjects affected / exposed	0 / 37 (0.00%)	0 / 36 (0.00%)	1 / 70 (1.43%)
occurrences (all)	0	0	1
Gingivitis			
subjects affected / exposed	1 / 37 (2.70%)	0 / 36 (0.00%)	0 / 70 (0.00%)
occurrences (all)	1	0	0
Pyuria			
subjects affected / exposed	0 / 37 (0.00%)	0 / 36 (0.00%)	1 / 70 (1.43%)
occurrences (all)	0	0	1
Sinusitis			
subjects affected / exposed	0 / 37 (0.00%)	0 / 36 (0.00%)	2 / 70 (2.86%)
occurrences (all)	0	0	2
Tooth infection			
subjects affected / exposed	0 / 37 (0.00%)	1 / 36 (2.78%)	0 / 70 (0.00%)
occurrences (all)	0	1	0
Upper respiratory tract infection			
subjects affected / exposed	6 / 37 (16.22%)	3 / 36 (8.33%)	6 / 70 (8.57%)
occurrences (all)	6	3	6
Urinary tract infection			
subjects affected / exposed	0 / 37 (0.00%)	0 / 36 (0.00%)	2 / 70 (2.86%)
occurrences (all)	0	0	2
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 37 (0.00%)	0 / 36 (0.00%)	1 / 70 (1.43%)
occurrences (all)	0	0	1
Metabolism and nutrition disorders			

Glucose tolerance impaired			
subjects affected / exposed	0 / 37 (0.00%)	0 / 36 (0.00%)	1 / 70 (1.43%)
occurrences (all)	0	0	1
Hypertriglyceridaemia			
subjects affected / exposed	1 / 37 (2.70%)	0 / 36 (0.00%)	1 / 70 (1.43%)
occurrences (all)	1	0	1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
07 October 2009	Addition of fasting requirements before site visits when blood and urine samples would be collected for safety laboratory testing.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

On 26 May 2010, the study was stopped due to statistical evidence of pre-defined futility.

Notes: