



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 (\geq) 65 years | 8 | 24 | |
|----------------------------------------------|---|----|--|

| | | | |
|---------------------------------------|----|----|--|
| Gender categorical Units: Subjects | | | |
| Female | 13 | 43 | |
| Male | 6 | 31 | |

End points

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 Usage

| | |
|-----------------|-------------------------------------------------|
| End point title | Number of Subjects With Rescue Medication Usage |
|-----------------|-------------------------------------------------|

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 nanogram 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) | 0.7299 (\pm 1.0448) | | | |
| Post dose Day 36 (n= 18) | 99999 (\pm 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 (\pm 0.1) | 6.75 (\pm 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 orally 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 occurrences (all) | 1 / 37 (2.70%) 1 | 0 / 36 (0.00%) 0 | 1 / 70 (1.43%) 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 occurrences (all) | 0 / 37 (0.00%) 0 | 1 / 36 (2.78%) 1 | 0 / 70 (0.00%) 0 |
| Skin and subcutaneous tissue disorders | | | |
| Ecchymosis subjects affected / exposed occurrences (all) | 0 / 37 (0.00%) 0 | 0 / 36 (0.00%) 0 | 1 / 70 (1.43%) 1 |
| Hyperhidrosis subjects affected / exposed occurrences (all) | 0 / 37 (0.00%) 0 | 1 / 36 (2.78%) 1 | 0 / 70 (0.00%) 0 |
| Night sweats subjects affected / exposed occurrences (all) | 0 / 37 (0.00%) 0 | 0 / 36 (0.00%) 0 | 1 / 70 (1.43%) 1 |
| Rash subjects affected / exposed occurrences (all) | 0 / 37 (0.00%) 0 | 0 / 36 (0.00%) 0 | 1 / 70 (1.43%) 1 |
| Renal and urinary disorders | | | |
| Pollakiuria subjects affected / exposed occurrences (all) | 0 / 37 (0.00%) 0 | 1 / 36 (2.78%) 1 | 1 / 70 (1.43%) 1 |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia subjects affected / exposed occurrences (all) | 0 / 37 (0.00%) 0 | 1 / 36 (2.78%) 1 | 0 / 70 (0.00%) 0 |
| Back pain subjects affected / exposed occurrences (all) | 2 / 37 (5.41%) 2 | 2 / 36 (5.56%) 2 | 2 / 70 (2.86%) 2 |
| Bursitis subjects affected / exposed occurrences (all) | 0 / 37 (0.00%) 0 | 1 / 36 (2.78%) 2 | 0 / 70 (0.00%) 0 |
| Chondritis subjects affected / exposed occurrences (all) | 1 / 37 (2.70%) 1 | 0 / 36 (0.00%) 0 | 0 / 70 (0.00%) 0 |
| Musculoskeletal pain subjects affected / exposed occurrences (all) | 0 / 37 (0.00%) 0 | 1 / 36 (2.78%) 1 | 0 / 70 (0.00%) 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 occurrences (all) | 0 / 37 (0.00%) 0 | 0 / 36 (0.00%) 0 | 1 / 70 (1.43%) 1 |
| Hypertriglyceridaemia subjects affected / exposed occurrences (all) | 1 / 37 (2.70%) 1 | 0 / 36 (0.00%) 0 | 1 / 70 (1.43%) 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. |
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Notes: