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COMPOUND NUMBER: PF-04191834

PROTOCOL NO.: B0041007

PROTOCOL TITLE: A Phase 2 Randomized, Double-Blinded, Double-Dummy, Placebo and Active Controlled two Cohort two-way Cross-Over, Multi-Centre Clinical Trial to Examine the Pain Relief Produced by 2 Weeks of Daily Oral Administration of a 5-Lipoxygenase (5-LO) Inhibitor PF-04191834 Alone and in Combination With Naproxen in Patients With Flare-Enriched Osteoarthritis of the Knee

Study Centers: A total of 22 centers participated and randomized subjects to treatment in the study, including 16 centers in the United States, 4 in Canada, and 2 in Sweden.

Study Initiation and Final Completion Dates: 19 July 2010 to 16 February 2011. The study was terminated prematurely.

Phase of Development: Phase 2

Study Objectives:

Primary Objectives:

- To evaluate the efficacy of PF-04191834 versus (vs) placebo in relieving pain in subjects with osteoarthritis (OA) of the knee.
- To evaluate the efficacy of PF-04191834 plus naproxen vs naproxen in relieving pain in subjects with OA of the knee.
- To evaluate the safety and tolerability of PF-04191834 (as monotherapy) in subjects with OA.
- To evaluate the safety and tolerability of PF-04191834 when co-administered with naproxen in subjects with OA.

Secondary Objectives:

- To examine the pharmacokinetics (PK) of PF-04191834 in subjects with OA
- To explore the relationship between urinary Leukotriene E_4 (LTE_4) levels as a biomarker of 5-LO inhibition and efficacy of PF-04191834 in subjects with OA.

- To provide samples for exploratory research into the mechanism of action of PF-04191834 and/or the disease (OA) under study.

Study Design: This was a randomized, double-blind, double-dummy, 2-cohort placebo and active controlled crossover study to compare the efficacy and safety of PF-04191834 when dosed alone and in combination with naproxen compared to placebo and naproxen, respectively, in subjects with OA of the knee.

For each subject, the study consisted of 10 visits: 1 screening visit, a pre-randomization visit, 2 study periods, and 1 follow-up visit. Following screening, potential subjects receiving analgesic therapy, including over-the-counter pain medications and topical analgesics for OA pain, discontinued these therapies for the duration of the study, up to and including Visit 10. These subjects washed out from these medications for a minimum of 2 days and up to a maximum of 14 days prior to Visit 2 depending upon the type of medication administered. If subjects met the relevant randomization criteria, they were randomized to 1 of 4 treatment crossover sequence groups.

Subjects were assigned in a 1:1:1:1 ratio to 1 of the following 4 crossover treatment sequence groups.

Cohort 1:

- PF-04191834 followed by placebo.
- Placebo followed by PF-04191834.

Cohort 2:

- PF-04191834 + naproxen followed by naproxen.
- Naproxen followed by PF-04191834 + naproxen.

The dose of PF-04191834 was administered 600 mg twice daily (BID); the naproxen dose was 500 mg BID; and the PF-04191834 + naproxen dose was 600 mg + 500 mg, respectively, BID. All doses were to be taken in the fed state. Treatment periods were separated by a 2-week placebo washout.

Table 1 summarizes the schedule of activities.

Table 1. Schedule of Activities

Protocol Activity	Screen	Treatment Period 1				Treatment Period 2				Follow-Up[a]
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10
Study Day/Window	**D-21 to D-7**	**D-7**	**D1**	**D8±2**	**D15[b] +1**	**D22 ±2**	**D29,-1**	**D36 ±2**	**D43[c]+1**	**D50±2**
Informed consent	X									
Medical history	X									
Primary diagnosis/OA ACR criteria	X[d]									
Demography	X									
Body weight and height	X									
Physical examination	X									X
BP & pulse rate (sitting)	X	X	X	X	X	X	X	X	X	X
12-lead ECG (single)	X		X		X		X		X	X
Laboratory assessments										
Hematology	X		X		X		X		X	X
Chemistry	X	X	X	X	X	X	X	X	X	X
Urinalysis	X		X		X		X		X	X
Urine pregnancy test[e]	X		X		X		X		X	X
Serum FSH (NCP females only)	X									
Urine drug test (dipstick by site at Visit 3 only)	X		X		X		X		X	
HIV/hepatitis screen	X									
Pharmacodynamics/pharmacokinetics										
Phamacogenomics sampling[f]			X							
Urine sample for LTE4 and creatinine[g]		X	X	X	X	X	X	X	X	
Pharmacokinetic sample[h]			X	X	X	X	X	X	X	
Exploratory research sample (blood)		X	X			X	X			
Assessments										
Review entry criteria	X	X	X							
Randomization			X							
WOMAC Index (full)		X	X	X	X	X	X	X	X	
Hospital Anxiety & Depression Scale	X									
C-SSRS	X				X				X	
Issue NRS daily pain diary[i]	X									
Daily pain NRS	X[c]	X[j, k]	X	X	X	X	X	X	X	X
Review diary/medication compliance[l]		X	X	X	X	X	X	X	X	X
Concomitant Medications										
Concomitant medication review	X----------									----------X
Discontinue current pain medications, if applicable	X									
Dispense rescue medication	X	X		X		X		X		

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Study Day/Window	**D-21 to D-7**	**D-7**	**D1**	**D8±2**	**D15[b] +1**	**D22 ±2**	**D29,-1**	**D36 ±2**	**D43[c]+1**	**D50±2**
Record rescue medication use	X----------									----------X
Return rescue medication		X		X		X		X		X
Dispense study medication		X	X	X	X	X	X	X	X	
Return study medication			X	X	X	X	X	X	X	X
AE assessment	X----------									----------X

ACR = American College of Rheumatology; AE = adverse event; BP = Blood pressure; COX-2 = cyclooxygenase-2; C-SSRS = Columbia Suicide Severity Rating Scale; D = day; ECG = Electrocardiogram; FSH = follicle-stimulating hormone; HIV = human immunodeficiency virus; LTE4 = leukotriene E4; NCP = Non-childbearing potential; OA = Osteoarthritis; NRS = numeric rating scale; NSAID = nonsteroidal anti-inflammatory drug; SAEs = serious adverse events; Screen = screening; WOMAC = Western Ontario & McMaster.

a. Subjects were contacted by telephone within 28 days of Visit 10 to assess for SAEs and general condition after return to previous medication.
b. Was at least 14 days after Visit 3.
c. Was at least 14 days after Visit 7.
d. X-ray confirmation was required (a Kellegren-Lawrence X-ray grade of ≥2) with symptom duration of at least 3 months. X-ray taken of the index knee within the last 12 months could have been used for confirmation.
e. Women of childbearing potential only, except at Screening.
f. Sample was collected at randomization.
g. Obtained prior to dosing.
h. Predose and between 1 and 3 hour postdose.
i. The daily pain diary was issued at Screening and collected at every visit.
j. The 11-point NRS score was collected for all subjects at Screening. For subjects washing out from active analgesic therapies only, the 11-point NRS score was assessed following wash out. This could have been done at Visit 2, if appropriately timed, or by telephone contact.
k. The following criteria was met for randomization: Subjects completed the NRS on 5 of the preceding 7 days with a mean daily pain score ≥4 over the last 3 day's entries; subjects discontinued background NSAIDs and COX-2 inhibitors, an increase in NRS ≥1 during the placebo run-in was required; WOMAC pain subscore ≥6.
l. Included compliance for rescue and study medication.

Number of Subjects (Planned and Analyzed): A total of approximately 190 subjects were to be randomized to ensure 144 subjects completed the study (72 subjects/cohort, 36 subjects/treatment sequence). Seventy nine subjects were assigned to the PF-04191834 treatment group, 81 subjects were assigned to the PF-04191834/naproxen treatment group, 83 subjects were assigned to the naproxen treatment group, and 81 subjects were assigned to the placebo treatment group. At the time of study termination, 190 subjects were randomized in the study; 154 in United States, 33 in Canada, and 3 in Sweden.

Diagnosis and Main Criteria for Inclusion: Male or female subjects between the ages of 18 and 75 years inclusive with a diagnosis of osteoarthritis based on the American College of Rheumatology criteria confirmed by an x-ray, willing and able to discontinue all current analgesic therapy for the duration of the study. Subjects had to be willing and able to complete a daily pain diary.

Exclusion Criteria: Subjects with body mass index (BMI) of >39 kg/m^2 or known allergy or hypersensitivity to naproxen or with any condition or medical history that could interfere with the subject's ability to complete the study visits and assessments were exclude from the study.

Study Treatment: PF-04191834 and matching placebo were provided by the Sponsor as 100-mg tablets for oral administration, in 120-count bottles. Blinded naproxen and matching placebo were provided as 500-mg tablets for oral administration, in 20-count bottles. As instructed, subjects self-administered and recorded date and time of dosing in dosing diaries.

Subjects were provided by the Investigator with rescue medication (500 mg of paracetamol/acetaminophen to be taken as needed to a maximum of 4 doses per day or 2000 mg per day). This rescue medication had to be discontinued 48 hours prior to the baseline visit (Visit 3).

Efficacy Endpoints:

Primary Endpoint:

- Western Ontario & McMaster (WOMAC) Osteoarthritis Index (48 hour recall, categorical version) Pain Score (Likert Scale, Range 0-20) in the more painful knee joint as identified at Screening at the End of Treatment period relative to Baseline as follows:
    - PF-04191834 compared to placebo.
    - PF-04191834 + naproxen compared to naproxen.

Secondary Endpoints:

- WOMAC Stiffness domain score (Likert scale for 2 items, overall score ranges from 0-8).
- WOMAC Physical Function domain score (Likert scale for 17 items, overall score ranges from 0-68).

- WOMAC Total Score.
- Importance weighted Total WOMAC Score.
- Daily pain diary over Weeks 1 and 2 of each treatment period using an 11-point Numeric Rating Scale.
- Subjects' use of rescue medication.
- Summary of plasma concentrations of PF-04191834.
- Summary of urinary LTE_4 levels.

Safety Evaluations: Safety evaluations included clinical monitoring, vital signs (pulse rate, blood pressure), 12-lead electrocardiograms (ECGs), adverse events (AEs), physical examination, and safety laboratory tests. All subjects were assessed at the screening visit for potential suicide risk using the Columbia Suicide Severity Rating Scale (C-SSRS).

Statistical Methods: Full Analysis Set (FAS): This included all subjects randomized who had received at least 1 dose of study drug, regardless of whether they have efficacy data.

Per Protocol Set (PP): The PP population was defined prior to breaking the blind and included only those subjects who completed the study with no major protocol deviations. The PP population was used to conduct a secondary analysis of the primary endpoint (WOMAC pain score).

Safety Data Set: This population was defined as randomized subjects that took at least 1 dose of study medication.

Analysis of primary endpoint: The primary analysis was based on the FAS and the primary endpoint, the WOMAC pain subscore measured at Visits 5 and 9, with baseline measurements (Visits 3 and 7) incorporated as covariates.

The analysis for continuous endpoints was a mixed model using random subject effect and fixed period and treatment effects, which utilized the baseline scores (1 for each treatment period) as inter- and intra-subject covariates and the average of the 2 baselines as well as the difference from the average for each period respectively.

The primary treatment comparison was the difference between PF-04191834 and placebo. The adjusted treatment difference (PF-04191834 – placebo), 80% confidence interval (CI), standard error, and 1-sided p-values, were presented. In addition to the primary endpoint (WOMAC pain) the probability that the treatment difference was smaller than 0 and -1.8 was calculated to assess the efficacy of PF-04191834. The comparison between naproxen and naproxen plus PF-04191834 was calculated using a similar model and the probability that the treatment difference was <0 and –0.6 was presented.

Further mixed models were run on the data from 2 of the 4 treatment sequences separately corresponding to the 2-treatment 2-period crossover data sets.

Carry-over from Period 1 to the baseline of Period 2 was investigated by fitting an analysis of covariance (ANCOVA) to the Period 2 baseline measures. The ANCOVA had fixed effects for Period 1 treatment, and the baseline for Period 1 was fitted as a covariate.

Analysis of secondary endpoints: The primary analysis was repeated using the PP analysis set with the summary measures of the raw data and the mean plot for each sequence. Further sensitivity analyses on the primary endpoint were also completed.

The probability that this treatment difference was smaller (more negative) than 0 and -1.8 was calculated to assess the efficacy of PF-04191834 relative to placebo and current standard of care (estimated to be a difference from placebo of -1.8 after 2 weeks treatment) respectively. The comparison between naproxen and naproxen + PF-04191834 was analyzed and the probability that the treatment difference was smaller (more negative) than 0 and -0.6 was also calculated.

Responder analyses were run on all subjects from all 4 treatment sequence groups. This model assessed both a 30% and a 50% reduction in mean pain score during the treatment period. For each of the 2 models, the 1-sided p-value, odds ratio, and corresponding 80% CI for the respective treatment comparisons were presented.

The Baseline, Week 1, and Week 2 mean diary pain scores were reported by sequence and treatment using summary statistics of number, mean, standard deviation (SD), median, minimum, maximum, and change from Baseline.

Plasma concentrations of PF-04191834 in 10 subjects were summarized by treatment and time point using number, mean, SD, median, minimum, and maximum. The mean concentration by time was plotted by treatment.

Safety data were tabulated and presented by treatment group. No formal hypothesis testing was performed. C-SSRS was summarized by treatment and time using descriptive statistical methods.

RESULTS

The study was terminated prematurely on 24 December 2010 due to an SAE of "acute hepatitis" that, given the limited data available at the time, was considered likely to be study drug-related, and that could potentially alter the risk-benefit of the study medication for subjects remaining in the study. At the time of study termination, 190 subjects were randomized (full target randomization), received at least 1 dose of study treatment, and were included in the FAS.

Subject Disposition and Demography: All subjects were analyzed for safety and included in the PK analysis. A summary of data sets analyzed and the reason for discontinuation by treatment are shown in Table 2.

Table 2. Subject Evaluation Groups and Study Discontinuation With Reasons by Treatment Periods

Number (%) of Subjects	PF-04191834	PF-04191834 + Naproxen	Naproxen	Placebo
Assigned to study treatment 190				
Treated	79	81	83	81
Completed study	58 (73.4)	65 (80.2)	61 (73.5)	56 (69.1)
Discontinued[a]	21 (26.6)	16 (19.8)	22 (26.5)	25 (30.9)
Related to study drug	13 (16.5)	13 (16.0)	15 (18.1)	17 (21.0)
Adverse event	0 (0)	3 (3.7)	2 (2.4)	2 (2.5)
Other	13 (16.5)	10 (12.3)	13 (15.7)	15 (18.5)
Not related to study drug	8 (10.1)	3 (3.7)	7 (8.4)	8 (9.9)
Adverse event	0 (0)	0 (0)	2 (2.4)	3 (3.7)
Other	4 (5.1)	2 (2.5)	5 (6.0)	5 (6.2)
Subject no longer willing to participate	4 (5.1)	1 (1.2)	0 (0)	0 (0)
Analyzed for efficacy				
Full analysis set	79 (100.0)	81 (100.0)	83 (100.0)	81 (100.0)
Per protocol set	34 (43.0)	41 (50.6)	41 (49.4)	34 (42.0)

a. Discontinuations occurring outside the lag period were attributed to the last study treatment received.

Table 3 presents a summary of the demographic and baseline characteristics of the subjects enrolled in the study. Baseline subject characteristics were similar across treatment groups.

Table 3. Summary of Demographic and Baseline Characteristics

	PF-04191834 to Placebo (N=48)	Placebo to PF-04191834 (N=47)	PF-04191834 + Naproxen to Naproxen (N=47)	Naproxen to PF 04191834 +Naproxen (N=48)
Gender (n)				
Male	18	16	27	19
Female	30	31	20	29
Mean age, years	60.2	57.9	59.0	60.5
White	40	39	42	40
Mean weight, kg	86.5	89.3	85.0	87.9
Mean BMI, kg/m^2	30.9	32.0	29.3	30.5
WOMAC Pain domain				
Mean score[a]	11.3	11.5	10.8	11.1

BMI = body mass index; N = number of subjects; n = number of subjects meeting specified criteria; WOMAC = Western & Ontario McMaster.

a. The WOMAC Pain subscale scores for each question range from 0 to 4, with higher scores indicating more pain.

Efficacy Results: For PF-04191834, the probabilities of having a greater reduction in pain than 0 and 1.8 relative to placebo are 0.067 and <0.0001, respectively (Table 4).

Table 4. Probability of Having a Greater Reduction in Pain Than the Target Difference for PF-04191834 (Relative to Placebo) and for PF-04191834 + Naproxen (Relative to Naproxen)

	Probability (Difference <0)	Probability (Difference <-1.8)
PF-04191834	0.067	<0.0001
PF-04191834+ naproxen	0.701	-

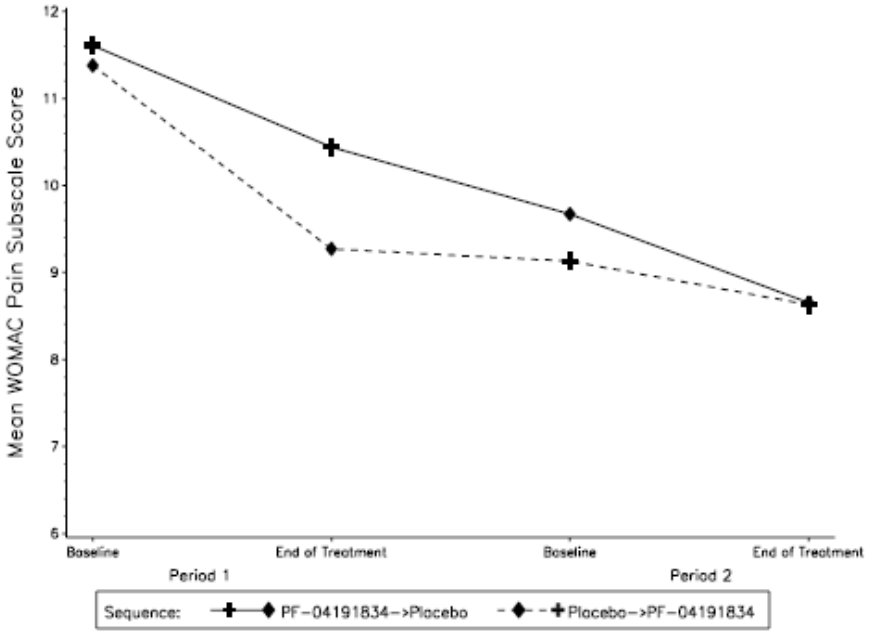
The observed mean WOMAC pain scores at each visit per treatment group are presented in Table 5 and Figure 1. A reduction in pain scores over time was seen across all treatment sequences. There was no evidence of carryover of the treatment from 1 period to the next.

Table 5. Observed Mean WOMAC Pain Scores for Each Sequence by Period

Sequence	Period 1			Period 2		
	Baseline	End of Treatment	Change From Baseline	Baseline	End of Treatment	Change From Baseline
PF-04191834→ placebo	11.3	10.3	-1.2	9.7	8.1	-1.8
Placebo→ PF-04191834	11.5	9.8	-1.6	8.6	8.4	-0.6
PF-04191834 + naproxen→naproxen	10.8	9.0	-1.9	9.7	7.6	-1.5
Naproxen→PF-04191834 + naproxen	11.1	9.4	-1.6	10.2	8.2	-2.1

WOMAC = Western & Ontario McMaster.

Figure 1. Line Plot of Mean WOMAC Pain Subscale Score Over Time by Sequence (PPAS)



PPAS = Per Protocol analysis set; WOMAC = Western Ontario & McMaster.

Summary of WOMAC stiffness subscale scores at the End of Treatment is presented in Table 6.

Table 6. Summary of WOMAC Stiffness Subscale Score at End of Treatment by Sequence and Treatment (FAS)

Visits	Placebo→PF-04191834		PF-04191834→Placebo	
	Placebo (N=47)	PF-04191834 (N=31)	PF-04191834 (N=48)	Placebo (N=34)
Baseline				
n	47	29	48	33
Mean (SD)	5.0 (1.41)	3.9 (1.33)	4.8 (1.20)	4.2 (1.51)
Median (min, max)	5.0 (2.0, 8.0)	4.0 (1.0, 6.0)	5.0 (2.0, 7.0)	4.0 (0.0, 7.0)
End of treatment				
n	37	24	45	28
Mean (SD)	4.4 (1.44)	3.5 (1.38)	4.4 (1.28)	3.3 (1.65)
Median (min, max)	4.0 (2.0, 8.0)	4.0 (1.0, 6.0)	4.0 (1.0, 7.0)	4.0 (0.0, 6.0)
Change from Baseline				
n	37	23	45	27
Mean (SD)	-0.6 (1.57)	-0.4 (1.12)	-0.5 (1.18)	-1.0 (1.19)
Median (min, max)	-1.0 (-4.0, 3.0)	0.0 (-2.0, 2.0)	0.0 (-3.0, 2.0)	-1.0 (-4.0, 1.0)

Visits	PF-04191834/Naproxen→ Naproxen		Naproxen→ PF-04191834/Naproxen	
	PF-04191834/ Naproxen (N=47)	Naproxen (N=35)	Naproxen (N=48)	PF-04191834/ Naproxen (N=34)
Baseline				
n	47	32	48	32
Mean (SD)	4.7 (1.42)	3.9 (1.44)	4.8 (1.47)	4.4 (1.41)
Median (min, max)	5.0 (2.0, 8.0)	4.0 (0.0, 6.0)	5.0 (1.0, 8.0)	5.0 (1.0, 7.0)
End of treatment				
n	40	27	44	29
Mean (SD)	3.8 (1.36)	2.9 (1.31)	4.0 (1.55)	3.6 (1.74)
Median (min, max)	4.0 (0.0, 6.0)	3.0 (0.0, 5.0)	4.0 (1.0, 7.0)	4.0 (0.0, 8.0)
Change from Baseline				
n	40	25	44	27
Mean (SD)	-1.0 (1.93)	-0.8 (1.26)	-0.8 (1.42)	-0.9 (1.33)
Median (min, max)	0.0 (-6.0, 2.0)	0.0 (-3.0, 2.0)	0.0 (-4.0, 2.0)	-1.0 (-5.0, 1.0)

n was the total number of subjects contributing to the mean.
N was the number of subjects in the indicated population.
Baseline was the predose assessment on Visit 3 for Period 1 and Visit 7 for Period 2.
End of Treatment was defined as Visit 5 for Period 1 and Visit 9 for Period 2.
FAS = full analysis set; min = minimum; max = maximum; SD = standard deviation.

Summary of WOMAC physical function subscale score at the End of Treatment is presented in Table 7.

Table 7. Summary of WOMAC Physical Function Subscale Score at End of Treatment by Sequence and Treatment (FAS)

Visits	Placebo→PF-04191834		PF-04191834→Placebo	
	Placebo (N=47)	PF-04191834 (N=31)	PF-04191834 (N=48)	Placebo (N=34)
Baseline				
n	46	28	48	33
Mean (SD)	39.7 (10.27)	31.6 (9.64)	37.7 (9.39)	32.6 (12.37)
Median (min, max)	38.5 (13.0, 61.0)	33.0 (7.0, 51.0)	37.5 (16.0, 57.0)	34.0 (0.0, 65.0)
End of treatment				
n	36	24	45	28
Mean (SD)	35.7 (10.01)	30.8 (11.02)	35.4 (9.60)	27.9 (13.11)
Median (min, max)	35.0 (17.0, 65.0)	30.5 (12.0, 51.0)	37.0 (6.0, 49.0)	28.5 (0.0, 48.0)
Change from Baseline				
n	35	22	45	27
Mean (SD)	-3.7 (10.51)	-2.0 (7.30)	-3.2 (6.87)	-4.4 (7.57)
Median (min, max)	-1.0 (-34.0, 15.0)	0.0 (-17.0, 9.0)	-2.0 (-15.0, 9.0)	-1.0 (-21.0, 5.0)
Visits	**PF-04191834/Naproxen→Naproxen**		**Naproxen→PF-04191834/Naproxen**	
	PF-04191834/ Naproxen (N=47)	Naproxen (N=35)	Naproxen (N=48)	PF-04191834/ Naproxen (N=34)
Baseline				
n	47	31	45	31
Mean (SD)	37.4 (8.50)	31.6 (10.70)	38.7 (10.43)	35.6 (11.46)
Median (min, max)	38.0 (18.0, 68.0)	33.0 (2.0, 51.0)	39.0 (7.0, 60.0)	38.0 (8.0, 61.0)
End of treatment				
n	39	27	43	28
Mean (SD)	30.8 (11.30)	25.0 (10.75)	32.0 (13.43)	28.7 (14.95)
Median (min, max)	33.0 (3.0, 52.0)	25.0 (0.0, 44.0)	34.0 (3.0, 60.0)	29.5 (2.0, 63.0)
Change from Baseline				
n	39	25	41	26
Mean (SD)	-6.5 (10.52)	-5.1 (10.08)	-5.5 (9.51)	-7.8 (10.10)
Median (min, max)	-5.0 (-39.0, 8.0)	-2.0 (-32.0, 13.0)	-3.0 (-34.0, 11.0)	-5.5 (-40.0, 5.0)

n was the total number of subjects contributing to the mean.
N was the number of subjects in the indicated population.
Baseline was the predose assessment on Visit 3 for Period 1 and Visit 7 for Period 2.
End of Treatment was defined as Visit 5 for Period 1 and Visit 9 for Period 2.
FAS = full analysis set; min = minimum; max = maximum; SD = standard deviation.

Summary of WOMAC total scores at the End of Treatment is presented in Table 8.

Table 8. Summary of WOMAC Total Score at End of Treatment by Sequence and Treatment (FAS)

Visit	Placebo→PF-04191834		PF-04191834→Placebo	
	Placebo (N=47)	PF-04191834 (N=31)	PF-04191834 (N=48)	Placebo (N=34)
Baseline				
n	46	28	48	33
Mean (SD)	56.0 (13.49)	44.2 (13.62)	53.7 (11.96)	46.4 (16.94)
Median (min, max)	54.5 (23.0, 84.0)	46.0 (9.0, 72.0)	52.5 (31.0, 80.0)	48.0 (0.0, 91.0)
End of treatment				
n	36	24	45	28
Mean (SD)	49.9 (14.16)	42.6 (15.73)	50.0 (12.60)	39.4 (18.13)
Median (min, max)	48.5 (24.0, 93.0)	42.5 (17.0, 72.0)	51.0 (14.0, 69.0)	41.0 (0.0, 67.0)
Change from Baseline				
n	35	22	45	27
Mean (SD)	-5.9 (14.62)	-2.9 (10.48)	-4.8 (9.67)	-7.2 (10.52)
Median (min, max)	-2.0 (-48.0, 19.0)	-2.5 (-24.0, 14.0)	-3.0 (-25.0, 9.0)	-2.0 (-29.0, 4.0)
Visit	**PF-04191834/Naproxen→Naproxen**		**Naproxen→PF-04191834/Naproxen**	
	PF-04191834/ Naproxen (N=47)	Naproxen (N=35)	Naproxen (N=48)	PF-04191834/ Naproxen (N=34)
Baseline				
n	47	31	45	31
Mean (SD)	52.9 (11.57)	45.1 (14.37)	54.8 (14.05)	50.3 (15.96)
Median (min, max)	54.0 (30.0, 96.0)	48.0 (6.0, 72.0)	56.0 (15.0, 87.0)	52.0 (10.0, 86.0)
End of treatment				
n	39	27	43	28
Mean (SD)	43.5 (14.96)	35.4 (14.32)	45.4 (18.54)	40.6 (20.99)
Median (min, max)	43.0 (6.0, 73.0)	36.0 (0.0, 60.0)	50.0 (8.0, 84.0)	41.5 (3.0, 90.0)
Change from Baseline				
n	39	25	41	26
Mean (SD)	-9.3 (14.53)	-7.4 (14.53)	-7.9 (12.95)	-10.7 (13.92)
Median (min, max)	-7.0 (-50.0, 14.0)	-4.0 (-46.0, 21.0)	-5.0 (-47.0, 17.0)	-7.5 (-57.0, 5.0)

n was the total number of subjects contributing to the mean.
N was the number of subjects in the indicated population.
Baseline was the predose assessment on Visit 3 for Period 1 and Visit 7 for Period 2.
End of Treatment was defined as Visit 5 for Period 1 and Visit 9 for Period 2.
FAS = full analysis set; min = minimum; max = maximum; SD = standard deviation.

Summary of WOMAC importance weighted total score is presented in Table 9.

Table 9. Summary of WOMAC Importance Weighted Total Score at End of Treatment by Sequence and Treatment (FAS)

Visit	Placebo→PF-04191834		PF-04191834→Placebo	
	Placebo (N=47)	PF-04191834 (N=31)	PF-04191834 (N=48)	Placebo (N=34)
Baseline				
n	46	28	48	33
Mean (SD)	20.5 (4.94)	16.2 (5.03)	19.7 (4.38)	17.0 (6.23)
Median (min, max)	19.9 (8.4, 30.6)	16.9 (3.2, 26.4)	19.3 (11.2, 29.3)	17.6 (0.0, 33.5)
End of treatment				
n	36	24	45	28
Mean (SD)	18.2 (5.22)	15.6 (5.79)	18.3 (4.60)	14.4 (6.65)
Median (min, max)	17.8 (8.8, 34.1)	15.7 (6.1, 26.4)	18.7 (5.2, 25.1)	15.0 (0.0, 24.5)
Change from Baseline				
n	35	22	45	27
Mean (SD)	-2.1 (5.34)	-1.0 (3.86)	-1.8 (3.56)	-2.6 (3.88)
Median (min, max)	-0.9 (-17.6, 6.8)	-0.6 (-8.8, 5.0)	-1.2 (-9.1, 3.3)	-0.8 (-10.7, 2.0)
Visit	**PF-04191834/Naproxen→Naproxen**		**Naproxen→PF-04191834/Naproxen**	
	PF-04191834/ Naproxen (N=47)	Naproxen (N=35)	Naproxen (N=48)	PF-04191834/ Naproxen (N=34)
Baseline				
n	47	31	45	31
Mean (SD)	19.4 (4.26)	16.6 (5.25)	20.1 (5.17)	18.4 (5.88)
Median (min, max)	19.5 (10.4, 35.2)	17.5 (2.4, 26.4)	20.3 (5.5, 31.9)	19.2 (3.6, 31.6)
End of treatment				
n	39	27	43	28
Mean (SD)	15.9 (5.51)	13.0 (5.29)	16.6 (6.82)	14.9 (7.71)
Median (min, max)	15.9 (2.4, 26.8)	13.0 (0.0, 22.2)	18.2 (2.8, 30.8)	15.2 (1.2, 33.0)
Change from Baseline				
n	39	25	41	26
Mean (SD)	-3.4 (5.29)	-2.7 (5.39)	-2.9 (4.77)	-3.9 (5.11)
Median (min, max)	-2.4 (-18.4, 5.3)	-1.2 (-17.1, 7.7)	-1.7 (-17.2, 6.4)	-2.8 (-20.9, 1.9)

n was the total number of subjects contributing to the mean.
N was the number of subjects in the indicated population.
Baseline was the predose assessment on Visit 3 for Period 1 and Visit 7 for Period 2.
End of Treatment was defined as Visit 5 for Period 1 and Visit 9 for Period 2.
FAS = full analysis set; min = minimum; max = maximum; SD = standard deviation.

Summaries of mean diary pain scores during Weeks 1 and 2 are presented in Table 10 and Table 11, respectively.

Table 10. Summary of Mean Diary Pain Score During Week 1 by Sequence and Treatment (FAS)

Visits	Placebo→PF-04191834		PF-04191834→Placebo	
	Placebo (N=47)	PF-04191834 (N=31)	PF-04191834 (N=48)	Placebo (N=34)
Baseline				
n	47	31	48	33
Mean (SD)	6.9 (1.36)	4.8 (2.31)	6.5 (1.56)	5.1 (2.18)
Median (min, max)	6.8 (4.0, 10.0)	4.8 (0.8, 8.5)	6.5 (4.0, 10.0)	5.3 (0.3, 10.0)
Week 1				
n	47	31	47	34
Mean (SD)	6.5 (1.52)	4.8 (2.48)	6.2 (1.71)	5.1 (2.27)
Median (min, max)	6.6 (3.0, 9.0)	5.0 (0.0, 9.1)	6.1 (2.4, 9.0)	5.0 (0.0, 9.0)
Change from Baseline				
n	47	31	47	33
Mean (SD)	-0.3 (1.00)	-0.0 (0.87)	-0.3 (1.02)	-0.2 (0.74)
Median (min, max)	-0.3 (-4.0, 2.0)	0.0 (-1.7, 2.6)	-0.1 (-3.3, 1.9)	-0.3 (-2.0, 2.0)
Visits	**PF-04191834/Naproxen→Naproxen**		**Naproxen→PF-4191834/Naproxen**	
	PF-04191834/ Naproxen (N=47)	Naproxen (N=35)	Naproxen (N=48)	PF-04191834/ Naproxen (N=34)
Baseline				
n	47	35	48	34
Mean (SD)	6.4 (1.45)	5.4 (1.69)	6.7 (1.55)	5.6 (1.85)
Median (min, max)	6.5 (3.0, 9.8)	5.0 (2.3, 9.0)	6.8 (4.0, 9.8)	5.6 (2.0, 9.5)
Week 1				
n	47	35	48	34
Mean (SD)	5.4 (1.80)	4.7 (1.87)	5.6 (2.05)	5.0 (2.04)
Median (min, max)	5.4 (1.0, 9.0)	4.9 (0.0, 8.4)	5.4 (2.0, 9.4)	4.5 (1.7, 9.6)
Change from Baseline				
n	47	35	48	34
Mean (SD)	-0.9 (1.65)	-0.6 (1.20)	-1.1 (1.64)	-0.6 (1.03)
Median (min, max)	-0.6 (-5.6, 2.6)	-0.4 (-4.0, 1.0)	-0.6 (-6.1, 1.8)	-0.3 (-3.5, 1.1)

n was the total number of subjects contributing to the mean.
N was the number of subjects in the indicated population.
Baseline was defined as the average of the last 4 days prior to Visits 3 and 7 and the pre-treatment entry on these visits.
Week 1 was defined as the average of the first 7 days after Visits 3 and 7.
FAS = full analysis set; min = minimum; max = maximum; SD = standard deviation.

Table 11. Summary of Mean Diary Pain Score During Week 2 by Sequence and Treatment (FAS)

Visits	Placebo→PF-4191834		PF-04191834→Placebo	
	Placebo (N=47)	PF-04191834 (N=31)	PF-04191834 (N=48)	Placebo (N=34)
Baseline				
n	47	31	48	33
Mean (SD)	6.9 (1.36)	4.8 (2.31)	6.5 (1.56)	5.1 (2.18)
Median (min, max)	6.8 (4.0, 10.0)	4.8 (0.8, 8.5)	6.5 (4.0, 10.0)	5.3 (0.3, 10.0)
Week 2				
n	39	31	38	34
Mean (SD)	5.8 (1.72)	4.5 (2.58)	5.8 (1.91)	4.8 (2.44)
Median (min, max)	6.0 (2.5, 9.0)	4.5 (0.0, 9.0)	5.9 (1.7, 9.0)	4.8 (0.0, 9.0)
Change from Baseline				
n	39	31	38	33
Mean (SD)	-0.9 (1.24)	-0.3 (1.20)	-0.7 (1.27)	-0.4 (1.02)
Median (min, max)	-0.7 (-4.0, 2.0)	-0.3 (-2.8, 3.5)	-0.6 (-3.9, 2.8)	-0.3 (-3.0, 2.2)
Visits	**PF-04191834/Naproxen->Naproxen**		**Naproxen->PF-04191834/Naproxen**	
	PF-04191834/ Naproxen (N=47)	Naproxen (N=35)	Naproxen (N=48)	PF-04191834/ Naproxen (N=34)
Baseline				
n	47	35	48	34
Mean (SD)	6.4 (1.45)	5.4 (1.69)	6.7 (1.55)	5.6 (1.85)
Median (min, max)	6.5 (3.0, 9.8)	5.0 (2.3, 9.0)	6.8 (4.0, 9.8)	5.6 (2.0, 9.5)
Week 2				
n	42	34	41	34
Mean (SD)	5.3 (1.66)	4.4 (1.68)	5.6 (2.16)	4.8 (2.18)
Median (min, max)	5.6 (2.5, 9.0)	4.5 (0.0, 7.7)	5.8 (1.8, 10.0)	4.4 (1.0, 9.5)
Change from Baseline				
n	42	34	41	34
Mean (SD)	-0.9 (1.44)	-0.9 (1.58)	-1.0 (1.60)	-0.8 (1.20)
Median (min, max)	-0.8 (-4.3, 2.3)	-0.5 (-7.6, 1.0)	-1.0 (-5.2, 1.5)	-0.7 (-3.8, 0.7)

n was the total number of subjects contributing to the mean.
N was the number of subjects in the indicated population.
Baseline was defined as the average of the last 4 days prior to Visits 3 and 7 and the pre-treatment entry on these visits.
Week 2 was defined as the average of the 6 days prior to Visits 5 and 9 and the morning of these visits.
FAS = full analysis set; min = minimum; max = maximum; SD = standard deviation.

Rescue medication use is summarized in Table 12.

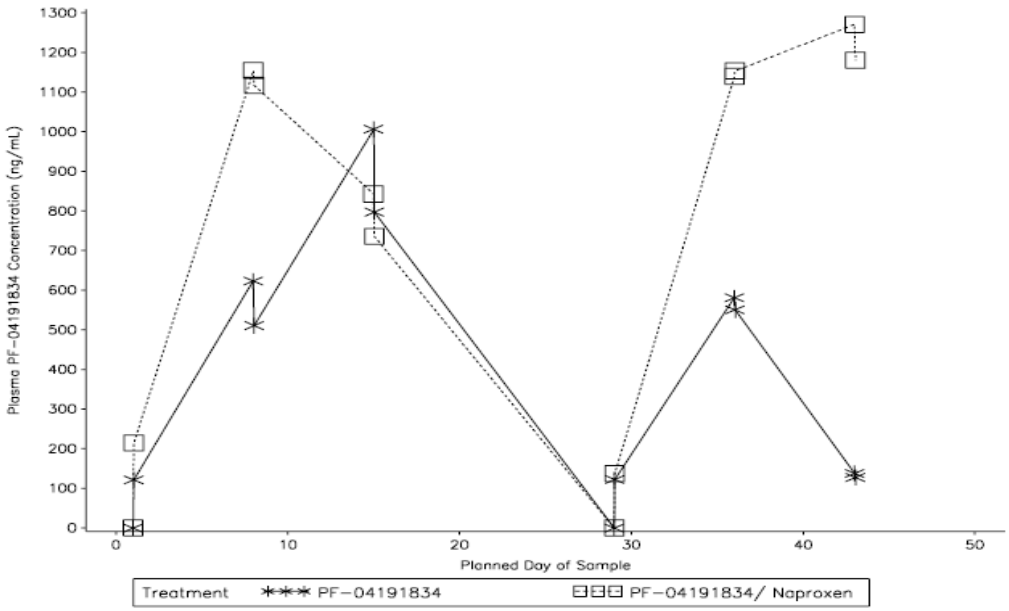
Table 12. Summary of Rescue Medication Use by Sequence and Treatment

Parameters	Placebo→PF-04191834		PF-04191834→Placebo	
	Placebo (N=47)	PF-04191834 (N=31)	PF-04191834 (N=48)	Placebo (N=34)
n	30	16	33	20
Mean (SD)	1114.5 (367.92)	1078.1 (200.62)	1096.1 (310.59)	1100.0 (528.15)
Median (min, max)	1000 (500, 2000)	1000 (750, 1500)	1000 (500, 2000)	1000 (500, 2500)
	PF-04191834/Naproxen→Naproxen		Naproxen→PF-04191834/Naproxen	
	PF-04191834/ Naproxen (N=47)	Naproxen (N=35)	Naproxen (N=48)	PF-04191834/ Naproxen (N=34)
n	26	13	26	13
Mean (SD)	1210.2 (442.70)	980.8 (360.29)	1073.7 (409.83)	932.7 (263.27)
Median (min, max)	1000 (500, 2250)	1000 (500, 2000)	1000 (500, 2000)	1000 (500, 1500)

n was the total number of subjects contributing to the mean.
N was the number of subjects in the indicated population.
min = minimum; max = maximum; SD = standard deviation.

Mean plasma PF-04191834 concentration-time profiles by treatment are presented in Figure 2. Due to early termination of the study, only a subset of PK samples, from 10 out of 190 randomized subjects, were selected for analysis. These 10 subjects were selected based on treatment and treatment sequence. Among them, 5 subjects had elevation of liver enzymes and the other 5 subjects did not. All 10 subjects selected for PK had detectable PF-04191834 concentrations during the treatment period. There was no evidence to suggest subjects with liver function test (LFT) elevation(s) had greater than expected exposure based on this limited PK data.

Figure 2. Mean Plasma PF-04191834 Concentration-Time Profiles Following Oral PF-04191834 (600 mg BID) or PF-04191834 (600 mg BID) With Naproxen (500 mg BID) Dose



BID = twice daily.

Since the study was terminated prematurely due to a potential safety concern, and in light of the efficacy analysis, the PD assessment of $uLTE_4$ was not performed.

Safety Results: A summary of treatment-emergent AEs is presented in Table 13. The number of AEs across treatment groups was similar.

Table 13. Treatment-Emergent Non Serious Adverse Events by System Organ Class and Preferred Term (All Causalities) for Events Having a Frequency Rate ≥5%

System Organ Class and MedDRA Preferred Term	PF-04191834 n (%)	PF-04191834/ Naproxen n (%)	Naproxen n (%)	Placebo n (%)
Number (%) of subjects:				
Evaluable for adverse events	79	81	83	81
With adverse events	35 (44.3)	39 (48.1)	42 (50.6)	43 (53.1)
Gastrointestinal disorders	7 (8.9)	15 (18.5)	13 (15.7)	9 (11.1)
Diarrhoea	0	2 (2.5)	5 (6.0)	3 (3.7)
Nausea	1 (1.3)	5 (6.2)	2 (2.4)	0
Infections and infestations	12 (15.2)	8 (9.9)	8 (9.6)	12 (14.8)
Nasopharyngitis	4 (5.1)	2 (2.5)	2 (2.4)	1 (1.2)
Upper respiratory tract infection	4 (5.1)	2 (2.5)	2 (2.4)	5 (6.2)
Musculoskeletal and connective tissue disorders	11 (13.9)	9 (11.1)	9 (10.8)	14 (17.3)
Back pain	3 (3.8)	1 (1.2)	2 (2.4)	5 (6.2)
Nervous system disorders	9 (11.4)	6 (7.4)	10 (12.0)	6 (7.4)
Headache	6 (7.6)	5 (6.2)	8 (9.6)	5 (6.2)

Subjects were only counted once per treatment for each row.
Includes data up to 14 days after last dose of study drug.
MedDRA (version 14.0) coding dictionary applied.
MedDRA = Medical Dictionary for Regulatory Activities; n = subjects with AEs.

Table 14 summarizes treatment-emergent AEs by body system and preferred term. The most frequent AEs were headache, which occurred in similar frequency in all treatment groups (including placebo); gastrointestinal AEs (diarrhea and nausea), which occurred more frequently in naproxen-containing arms; and infections (nasopharyngitis and upper respiratory tract infection), which occurred in similar frequency in all treatment groups (which is not unexpected due to the timing of the study).

Table 14. Incidence of Treatment-Emergent Adverse Events in ≥2 Subjects in Any Treatment Group - All Causality (Treatment-Related)

System Organ Class MedDRA Preferred Term[a]	n, All Causality (Treatment-Related) PF-04191834 (N=79)	 PF-04191834/Naproxen (N=81)	 Naproxen (N=83)	 Placebo (N=81)
Gastrointestinal Disorders	7 (3)	16 (15)	13 (9)	9 (5)
Abdominal discomfort	0	2 (1)	0	0
Abdominal pain	0	3 (3)	2 (2)	0
Abdominal pain upper	0	3 (3)	0	1 (0)
Constipation	2 (2)	3 (2)	3 (3)	4 (4)
Diarrhoea	0	2 (2)	5 (2)	3 (0)
Dyspepsia	1 (0)	1 (1)	3 (3)	1 (1)
Nausea	1 (0)	5 (5)	2 (2)	0
General Disorders and Administration Site Conditions	5 (2)	2 (2)	1 (1)	2 (0)
Fatigue	2 (1)	1 (1)	1 (1)	0
Infections and Infestations	12 (1)	8 (0)	8 (0)	12 (0)
Bronchitis	0	2 (0)	1 (0)	1 (0)
Influenza	1 (0)	2 (0)	1 (0)	0
Nasopharyngitis	4 (0)	2 (0)	2 (0)	1 (0)
Upper respiratory tract infection	4 (1)	2 (0)	2 (0)	5 (0)
Injury, Poisoning and Procedural Complications	0	2 (0)	5 (0)	3 (0)
Fall	0	0	2 (0)	0
Investigations	1 (0)	4 (2)	1 (1)	5 (4)
Alanine aminotransferase increased	0	0	0	2 (1)
Electrocardiogram QT prolonged	0	0	0	2 (2)
Musculoskeletal and Connective Tissue Disorders	11 (0)	9 (1)	9 (0)	14 (0)
Arthralgia	3 (0)	0	2 (0)	3 (0)
Arthritis	3 (0)	0	0	3 (0)
Back pain	3 (0)	1 (0)	2 (0)	5 (0)
Musculoskeletal pain	0	3 (0)	3 (0)	1 (0)
Myalgia	0	3 (1)	0	0
Pain in extremity	1 (0)	2 (0)	2 (0)	1 (0)
Nervous System Disorders	9 (2)	6 (5)	10 (5)	7 (0)
Dizziness	1 (0)	2 (2)	1 (1)	0
Headache	6 (2)	5 (4)	8 (3)	5 (0)
Somnolence	1 (0)	0	2 (2)	0
Psychiatric Disorders	2 (0)	2 (2)	2 (1)	1 (0)
Insomnia	2 (0)	1 (1)	1 (1)	1 (0)
Renal and Urinary Disorders	0	1 (0)	2 (0)	0
Haematuria	0	1 (0)	2 (0)	0
Respiratory, Thoracic and Mediastinal Disorders	5 (0)	4 (3)	3 (1)	7 (0)
Dyspnoea	0	2 (2)	0	0
Nasal congestion	2 (0)	2 (1)	2 (1)	1 (0)
Oropharyngeal pain	3 (0)	0	1 (0)	4 (0)

If the same subject in a given treatment had >1 occurrence in the same preferred term event category, only the most severe occurrence was taken. Subjects were counted only once per treatment in each row. Includes all data collected since the first dose of study drug. MedDRA (version 14.0) coding was applied.
AEs and SAEs are not separated out in this table.
AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; N = total number of subjects in each treatment group; n = subjects with AEs; SAEs = serious adverse event.
a. Adverse event preferred terms were included if reported by >1 subject in any treatment.

Three subjects experienced SAEs, 2 of which (hemorrhagic gastric ulcer and acute hepatitis) the Investigator judged to be related to the study treatment. The hemorrhagic gastric ulcer was assessed as being likely due to naproxen (for which this is a recognized potential

complication). The acute hepatitis incident evolved into a suspected unexpected serious adverse reaction (SUSAR) as this was assessed as possibly a manifestation of DILI. As a result of this SUSAR, the Sponsor decided to terminate the study prematurely.

Table 15. Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term (All Causalities)

System Organ Class and MedDRA Preferred Term	PF-04191834 n (%)	PF-04191834/ Naproxen n (%)	Naproxen n (%)	Placebo n (%)
Number (%) of subjects:				
Evaluable for adverse events	79	81	83	81
With adverse events	0	2 (2.5)	0	1 (1.2)
Gastrointestinal disorders	0	1 (1.2)	0	0
Gastric ulcer haemorrhage	0	1 (1.2)	0	0
Hepatobiliary disorders	0	1 (1.2)	0	0
Hepatitis acute	0	1 (1.2)	0	0
Nervous system disorders	0	0	0	1 (1.2)
Syncope	0	0	0	1 (1.2)

Subjects were only counted once per treatment for each row.
Includes data up to 14 days after last dose of study drug.
MedDRA (version 14.0) coding dictionary applied.

Table 16 summarizes the permanent discontinuations due to AEs. Twelve subjects permanently discontinued from the study due to AEs (7 related, 5 unrelated). Two of the AEs were classified by the Investigator to be SAEs. All of the AEs that resulted in permanent discontinuations resolved.

Of these discontinuations, 13 in the PF-04191834 treatment group, 13 in the PF-04191834/naproxen treatment group, 15 in the naproxen treatment group, and 17 in the placebo treatment group were related to the study drug.

Table 16. Summary of Permanent Discontinuations due to Adverse Events

Serial Number	Sex/Age (Years)	Treatment at Onset	Treatment Phase	Preferred Term	Severity	Causality	Outcome
1	Female/59	Naproxen	Active	Thrombocytopenia	Mild	Unrelated	Resolved
2	Male/56	Placebo	Active	Alanine aminotransferase increased	Mild	Related	Resolved
			Post	Alanine aminotransferase increased	Mild	Related	Resolved
3	Female/66	Placebo	Active	Bronchitis	Mild	Unrelated	Resolved
4	Female/55	PF-04191834/Naproxen	Active	Vomiting	Severe	Related	Resolved
5	Female/50	Placebo	Active	Liver function test abnormal	Mild	Related	Resolved
			Post	Liver function test abnormal	Mild	Related	Resolved
6	Female/59	Naproxen	Active	Dyspepsia	Mild	Related	Resolved
7	Female/56	Naproxen	Active	Abdominal pain	Severe	Related	Resolved
8	Female/47	Naproxen	Active	Oropharyngeal pain	Moderate	Unrelated	Resolved
9	Male/61	PF-04191834/Naproxen	Active	Gastric ulcer heamorrhage	Severe	Related	Resolved
			Active	Haemoglobin decreased	Moderate	Unrelated	Resolved
			Active	Dyspnoea	Mild	Related	Resolved
			Active	Hyperhidrosis	Moderate	Related	Resolved
			Active	Hypotension	Moderate	Related	Resolved
10	Female/52	Placebo	Active	Syncope	Moderate	Unrelated	Resolved
11	Female/57	Placebo	Active	Back pain	Moderate	Unrelated	Resolved
12	Female/57	PF-04191834/Naproxen	Active	Anxiety	Moderate	Related	Resolved

MedDRA (version 14.0) coding dictionary applied.
MedDRA = Medical Dictionary for Regulatory Activities; SAE = serious adverse event (according to Investigator's assessment).

There were no deaths among subjects who participated in this study.

Other Safety Results: The most common laboratory test abnormalities were increases in blood urea nitrogen, uric acid (which were both present in each treatment group excluding placebo), and venous bicarbonate (which was present in each treatment group excluding PF-04191834/naproxen).

A total of 6 subjects ultimately met the individual stopping criteria for liver enzyme elevations (alanine aminotransferase [ALT] or aspartate aminotransferase ≥3 times upper limit of normal [ULN], or persistent or recurrent increases ≥1.5 times ULN). Of these, 2 were treated with PF-04191834 + naproxen, 3 were treated with placebo, and 1 was treated with PF-04191834. Upon further investigation, it was determined that 2 of the subjects (1 subject treated with placebo and 1 subject treated with PF-04191834) may have had an alternative explanation for elevated liver enzymes (alcohol consumption). The fourth subject met discontinuation criteria by having repeated elevations of ALT during treatment Period 1, with a peak ALT of approximately 2.5 times ULN. Upon further investigation, the subject admitted to having consumed a significant amount of alcohol at a wedding prior to the first event of ALT elevation.

No subjects who received PF-04191834 in the 2 cohorts met any of the post-baseline vital signs criteria for concern.

Four maximum increases from Baseline systolic blood pressure (BP; sitting) values of ≥30 mmHg were recorded (1 subject treated with placebo, 2 subjects treated with PF-04191834/naproxen, and 1 subject treated with PF-04191834). Three maximum increases from Baseline diastolic BP (sitting) values of ≥20 mmHg were recorded (2 subjects treated with placebo and 1 subject treated with naproxen). Five maximum decreases from Baseline systolic BP (sitting) values of ≥30 mmHg were recorded (2 subjects treated with placebo, 2 subjects treated with PF-04191834/naproxen, and 1 subject treated with naproxen). Five maximum decreases from Baseline diastolic BP (sitting) values of ≥20 mmHg were recorded (3 subjects treated with PF-04191834, 1 subjects treated with placebo, and 1 subject treated with naproxen).

One ≥60 msec increase in corrected QT interval (QTc) interval was seen in a subject treated with PF-04191834/naproxen. Three QTc interval increases (≥30, <60 mmHg) were seen in 1 subject treated with placebo and 2 subjects treated with naproxen.

No subjects met any physical finding criteria of concern.

There was 1 subject who had an AE report of "suicidal ideation" on spontaneous reporting. There was no change in the C-SSRS. This event was deemed to be a transient situational reaction and not a clinically significant event by a mental health professional.

CONCLUSIONS:

- In summary, PF-04191834 failed to demonstrate efficacy in the relief of knee OA pain as mono-therapy or on a background of standard of care nonsteroidal anti-inflammatory drug (naproxen) treatment at a dose expected to give full target coverage.

- The lack of a demonstrable effect of naproxen compared to placebo was unanticipated and complicates the assessment of efficacy of PF-04191834 in this trial.

- All 10 subjects selected for PK analysis had detectable PF-04191834 concentrations during the treatment period.

- PF-04191834 was generally safe and well tolerated, with the exception of liver enzyme elevations. There was 1 SAE of "acute hepatitis" that was considered likely to be study drug related and, in the absence of an alternative explanation, believed to represent a case of DILI. Understanding the true potential for PF-04191834 to cause clinically significant DILI would require further investigation.

- There was no evidence to suggest subjects with LFT elevation had greater than expected exposure based on this limited PK data.