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GENERIC DRUG NAME / COMPOUND NUMBER: Giripladib / PF-05236981 (PLA-695)

PROTOCOL NO.: 3175A1-202-WW (B3061017)

PROTOCOL TITLE: A Multicenter, Randomized, Double-Blind Comparison of 4 Dose Regimens of PLA-695, Naproxen, and Placebo Administered Daily for 6 Weeks in Subjects With Active Osteoarthritis of the Knee

Study Centers: Seventy-five (75) centers took part in the study: 14 in Canada; 35 in the United States; 5 in Hungary; 4 each in Poland; Spain, The Netherlands and Argentina, 1 each in Hong Kong and Brazil, 3 in Mexico and enrolled subjects.

Study Initiation and Final Completion Dates: November 2006 to November 2007

The study was terminated after the second interim analysis due to lack of efficacy.

Phase of Development: Phase 2

Study Objectives:

Primary Objectives:

- To assess the efficacy and safety of giripladib in subjects with active osteoarthritis (OA) of the knee.

Secondary Objectives:

- To determine the pharmacokinetic and pharmacodynamic (PD) of giripladib among dose levels.
- To assess health outcome measures.
- To assess giripladib exposure-response relationship on PD, efficacy, and safety measures.
- To assess pharmacogenomics associated with OA.

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METHODS

Study Design: This was a multicenter, randomized, double-blind, double-dummy, parallel, placebo- and positive-control (naproxen), dose-ranging study to assess the efficacy and safety of 3 oral doses of giripladib administered once daily (QD) and 1 dose of giripladib administered twice a day (BID) with food for 6 weeks. Subjects were randomly assigned to 1 of 6 treatment groups: giripladib 50 mg, 200 mg, or 400 mg QD, giripladib 200 mg BID, placebo, or naproxen 500 mg BID. It was estimated that subject enrollment would be completed within 8 months from the first subject enrolled in the study. The clinical portion of this study would be completed within approximately 11 months. The study flowchart is provided in Table 1.

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Table 1. Study Flowchart

Study Procedures	Days –14 to –1	Day 1	Week 1[a]	Week 2[a]	Week 3[a]	Week 4[a]	Week 5[a]	Week 6[a]	Early W/D	Final Visit[b]	Poststudy[c]
Study Interval	**Screening**	**Baseline**	**Treatment**							**Follow-Up**	
Informed consent	X										
Inclusion/exclusion criteria	X	X									
NSAID washout criteria met	X	X									
Demographics	X										
Medical history	X										
OA joint history	X										
For women, document history of non-childbearing potential[d]	X										
For sexually active men, document adequate birth control/contraception[e]	X	X	X	X	X	X	X	X	X	X	
Chest radiograph[f]	X										
Target knee radiograph[g]	X										
ECG (12-lead)	X							X	X		
Weight and height measurements[h]	X							X	X		
Physical examination	X	X	X	X	X	X	X	X	X	X	
Target knee examination	X	X	X	X	X	X	X	X	X	X	
Vital signs[i]	X	X	X	X	X	X	X	X	X	X	
Laboratory evaluations[j]	X	X	X	X	X	X	X	X	X	X	X
Serum β-HCG[j]	X	X						X	X	X	
HbsAg and HCV antibody[j]	X										
Helicobacter pylori serology[j]		X									
Blood NT-proBNP[j]		X		X				X	X[k]		
Urine CTX-II[j]		X						X	X[k]		
PK blood sample collection[l]			X			X			X		
Record prior medications/treatments	X	X									
Record concomitant medications/treatments			X	X	X	X	X	X	X	X	
WOMAC	X	X	X	X	X	X	X	X	X		
Investigators' overall assessment	X	X	X	X	X	X	X	X	X		
Joint tenderness	X	X	X	X	X	X	X	X	X		
Walking pain (categorical)	X	X	X	X	X	X	X	X	X		

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Study Interval	**Screening**	**Baseline**	**Treatment**							**Follow-Up**	
Subjects' overall assessment	X	X	X	X	X	X	X	X	X		
Subjects' assessment of arthritis pain (VAS)	X	X	X	X	X	X	X	X	X		
Duration of target knee stiffness		X		X				X	X		
Quality of sleep	X	X	X	X	X	X	X	X	X		
Night-time pain	X	X	X	X	X	X	X	X	X		
Subject preference	X	X	X	X	X	X	X	X	X		
EQ-5D General health VAS	X	X	X	X	X	X	X	X	X		
MOS sleep scale	X	X	X	X	X	X	X	X	X		
Fatigue VAS	X	X	X	X	X	X	X	X	X		
Dispense day 1 TA[m]		X									
Dispense weekly TA[n]		X	X	X	X	X	X				
TA capsule count/calculate compliance			X	X	X	X	X	X	X		
Dispense TA worksheet[o]		X			X						
Dispense subject information sheet	X	X									
Dispense weekly subject diary[p]		X	X	X	X	X	X				
Record adverse events[q]	X	X	X	X	X	X	X	X	X	X	X
Complete conclusion of phase form[r]								X	X		
Complete conclusion of subject participation form[s]										X[s]	X[s]

AE = adverse event; β-HCG = Beta-human chorionic gonadotropin, CTXII = Type II collagen c-telopeptides, HBsAg = hepatitis B surface antigen, HCV = hepatitis C virus, hs-CRP = high-sensitivity C-reactive protein, HDL = high-density lipoprotein, LDL = low-density lipoprotein, MOS = Medical Outcomes Study; NSAID = nonsteroidal anti-inflammatory drug, NT-proBNP = proB-type natriuretic peptide, PD = Pharmacodynamics, PGX = Pharmacogenomics; PK = pharmacokinetics, SAE = serious adverse event; TA = test article, TC = total cholesterol, TG = triglycerides, VAS = visual analog scale, WOMAC = Western Ontario and McMaster's Universities Osteoarthritis Index Version 3.1, W/D = withdrawal.

a. The Study Week 1 to 6 visits must occur within a window of 3 days from the Baseline Visit. The Week 1 to 5 visits must be scheduled so that the subject could receive the morning dose of TA at the study site at the same time of day (±2 hours) as the Baseline Visit. The Week 6 visit should be scheduled approximately the same time of day (±2 hours) as the Baseline Visit.
b. Final visit to be performed 15 to 22 days after the Week 6 (or earlyW/D) visit.
c. Subjects with AEs or abnormal laboratory test results at the Final Visit or within22 days after the last dose of TA were followed up by telephone call(s), site visit(s), and/or additional evaluation(s) until the event was subsided, returned to baseline, or in the case of permanent impairment, until the condition stabilized.

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Table 1. Study Flowchart

Study Procedures	Days –14 to –1	Day 1	Week 1[a]	Week 2[a]	Week 3[a]	Week 4[a]	Week 5[a]	Week 6[a]	Early W/D	Final Visit[b]	Poststudy[c]
Study Interval	**Screening**	**Baseline**	**Treatment**							**Follow-Up**	

d. Women must be of non-childbearing potential (ie, postmenopausal women with a documented history of amenorrhea for ≥12 months or women who were surgically sterile, such as after hysterectomy, bilateral oopherectomy, or tubal ligation [procedure performed at least 1 year before screening]).
e. For sexually active men, document adequate use of birth control/contraception at the Screening and Baseline Visits; document adequate use of birth control/contraception at the Week 1 through 6 (or earlyW/D) and final visits.
f. Chest radiograph might be performed at Screening if medically necessary to rule out exclusion criteria. A radiologist must read the chest radiograph report and a copy of the report must be available for review in the subject's source documents. Results of chest radiographs taken within 1 year before the Screening Visit might be used as long as there had not been any change to the subject's health status.
g. Weight-bearing anteroposterior and lateral views of the target knee must be read by a radiologist and the report must be available for review in the subject's source documents; radiographs taken within 1 year before the screening visit might be used as long as there had not been any changes in the clinical course of the disease.
h. Height was recorded at Screening only; body weight was recorded at Screening and Week 6 (or upon earlyW/D).
i. Blood pressure, pulse, and respiratory rate were recorded after the subject had been sitting for 5 minutes; also record oral or tympanic temperature (°F or °C).
j. Samples for these laboratory evaluations must be collected after an 8-hour fast**:** hematology, blood chemistry (including TC, LDL, HDL, TG, serum amylase, and serum lipase), routine urinalysis, urine CTXII (collected from the second morning void at Baseline and Week 6), hs-CRP, NT-proBNP (baseline, Week 2 and Week 6), HBsAg and HCV antibody (screening), *Helicobacter pylori* serology (baseline). A Serum pregnancy test (β-HCG) was to be performed in all women aged ≤55 years at Screening, Baseline, Week 6 (or upon early W/Dl), and at the Final Visit. Screening laboratory tests with abnormal results might be repeated once to confirm abnormal results. All screening laboratory results (including HBsAg and HCV), including any repeat laboratory tests, must be reviewed before randomization.
k. If the subject was withdrawn early, samples for NT-proBNP and CTX-II were collected only if TA was ingested within 1 day of the sample collection.
l. From at least half of the subjects, 2 PK blood samples (4 mL of blood collected for each plasma sample) was obtained at the following time points: PK1 was collected at Week 1 (6 to 23 hours after the evening dose of TA the night before the study visit); PK2 was collected at Week 4 (6 to 23 hours after the evening dose of TA the night before the study visit). The second PK blood sample might be collected at Week 6 or upon early withdrawal if not completed at Week 4.
m. Study personnel were administered TA with food on Baseline (Day 1) at the investigative site. The subject must be observed for 1 hour after ingestion of the first dose of TA. The date and time of any AEs occurring after administration of TA were recorded. The subjects were instructed to take the evening dose with food in the evening on Day 1.
n. The blister pack of TA was dispensed weekly. The subjects were instructed to take the morning dose and evening doses with food. At the Week 1 to 5 study visits, the morning dose of TA were administered with food to the subject at the site, after the completion of study procedures. The date and time of TA administration were recorded. The timing of the morning TA administration at the Week 1 to 5 study visits must be within a 2-hour window (the same time of day) as the time of TA ingestion at the Baseline Visit. TA was not administered at the Week 6 visit.
o. Dispense a TA worksheet to subjects at the Baseline (Day 1) and Week 3 visits. The subjects were instructed to record the date and exact time of the previous 2 days of morning and evening TA dose administration before the Week 1 and Week 4 study visits.
p. The weekly subject diary was dispensed at Baseline, and Weeks 1 through 5. The subjects were instructed to record the dosages of acetaminophen/paracetamol use between each study visit in the weekly diary. The diary was returned at each study visit. The acetaminophen/paracetamol used between study visits was transcribed.
q. AEs were recorded from the signing of the informed consent form to 15 days after the last dose of TA. If an AE or SAE continues, the Investigator must follow-up the event until it was subsided, returned to Baseline, or, in case of permanent impairment, until the condition stabilized.
r. Only 1 conclusion of phase form must be completed for each randomized subject at either the Week 6 or early W/D visit.
s. The conclusion of subject participation form was completed for all screen failure subjects; it will also be completed for those subjects that either complete or withdraw early from the study.

Number of Subjects (Planned and Analyzed): Approximately 560 subjects were planned to be enrolled and a total of 363 subjects enrolled and received at least 1 dose of test article were analyzed in the study.

Diagnosis and Main Criteria for Inclusion: Males and females, aged 50-75 years diagnosed with idiopathic OA of the knee for at least 3 months duration in accordance with [1986] American College of Rheumatology clinical and radiographic criteria: knee pain, the presence of osteophytes, and any one of the following: age >50 years, crepitus, or morning stiffness <30 minutes were included in the study. Subjects who got radiographic confirmation of OA at the target joint (weight-bearing anteroposterior and lateral views) within 1 year of screening, and must be currently treated for OA with a stable daily dose of 1 non-steroidal anti-inflammatory drug (NSAID) including cyclooxygenase-2 inhibitors, not exceeding the maximum recommended dose in the product label, and taken as prescribed by the physician, starting at least 4 weeks before the screening visit.

Exclusion Criteria: Subjects with history of or suspected current esophageal or gastrointestinal bleeding, ulcers, obstruction, or perforation, or pancreatitis, with Grade 4 severity on the Kellgren-Lawrence Scale on the screening target knee radiograph or with any clinically significant laboratory abnormality were excluded from the study.

Study Treatment: The study drug giripladib was provided as 50 mg and 100 mg capsules. Naproxen (comparator) was administered as 500 mg capsules. Matching placebos capsules were provided for both giripladib and naproxen orally. Each morning and evening dose contained 1 naproxen capsule. The morning and evening doses of study drug on Day 1 consisted of 4 and 2 study drug capsules and on the remaining days of treatment it comprised of 2 and 4 capsules in morning and evening respectively.

Each subjects' participation in the study was planned till 11 weeks. This included a 2 to 14 day washout period after discontinuation of previous NSAID, a 6-week double-blind study drug treatment period, and a required follow-up visit approximately 2 to 3 weeks after the Week 6 or early withdrawal visit.

Efficacy Endpoints:

Primary Endpoint: The primary efficacy endpoint for this study was the Western Ontario and McMaster's Universities Osteoarthritis Index (WOMAC) visual analog scale (VAS) walking pain (Question 1) at Week 6 of treatment

Secondary Efficacy Endpoints:

- WOMAC VAS walking pain at Weeks 1, 2, 3, 4, and 5
- WOMAC pain, stiffness and function subscales and composite score
- Investigators' efficacy evaluation, including overall assessment and joint tenderness

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- Subjects' efficacy evaluation, including walking pain (categorical), overall assessment, assessment of arthritis pain (VAS), duration of target knee stiffness (Baseline, Week 2, and Week 6), quality of sleep, night-time pain, subject preference; and weekly use of acetaminophen/paracetamol rescue medication

Safety Evaluations: Safety was evaluated from observed or spontaneously reported signs and symptoms, and the results of scheduled physical examination findings, body weight and vital sign measurements, 12-lead electrocardiogram (ECG) findings, screening chest radiographs, clinical laboratory evaluations, as well as elicited history reported by the subjects, premature withdrawals, adverse events (AEs), and serious adverse events (SAEs).

Statistical Methods: The analysis population set used in the study were:

- Modified Intent-to-Treat (mITT): It comprised of all randomized subjects all randomized subjects who received at least 1 dose of test article.

- Per-Protocol population: It was defined as a subset of mITT that had drug compliance ≥80% and did not have any major protocol deviations.

All efficacy and safety analyses were based on the mITT population. No analysis was done on the per-protocol population.

Change from Baseline to Week 6 in the WOMAC VAS walking pain was analyzed using analysis of covariance (ANCOVA) with Baseline score as a covariate and study treatment as a factor. Secondary endpoints and health outcomes considered as continuous were analyzed similarly.

Last observation carried forward method was used to impute missing data at a given time point. If no on-therapy value was available, baseline observation was carried forward.

For continuous safety variables such as vital signs and routine laboratory measurements, ANCOVA with baseline as the covariate and treatment group as a factor was performed. For discrete variables, such as premature withdrawals, treatment groups were compared using Fisher exact test.

RESULTS

Subject Disposition and Demography: The subject disposition is provided in Table 2 and the subject demography is provided in Table 3.

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Table 2. Conclusion of Subject Participation Summary, Safety Population

Conclusion Status Reason[a]	Placebo n=60	Giripladib 50 mg QD n=60	Giripladib 200 mg QD n=61	Giripladib 400 mg QD n=60	Giripladib 200 mg BID n=60	Naproxen 500 mg BID n=62	Total N=363
Total	60 (100)	60 (100)	61 (100)	60 (100)	60 (100)	62 (100)	363 (100)
Completed	36 (60.0)	41 (68.3)	36 (59.0)	43 (71.7)	35 (58.3)	38 (61.3)	229 (63.1)
Study completed	36 (60.0)	41 (68.3)	36 (59.0)	43 (71.7)	35 (58.3)	38 (61.3)	229 (63.1)
Discontinued	24 (40.0)	19 (31.7)	25 (41.0)	17 (28.3)	25 (41.7)	24 (38.7)	134 (36.9)
Adverse event	6 (10.0)	2 (3.3)	6 (9.8)	3 (5.0)	11 (18.3)	8 (12.9)	36 (9.9)
Discontinuation of study by sponsor	7 (11.7)	11 (18.3)	9 (14.8)	8 (13.3)	7 (11.7)	8 (12.9)	50 (13.8)
Failed to return	0	0	0	0	1 (1.7)	1 (1.6)	2 (0.6)
Lost to follow-up	1 (1.7)	0	0	1 (1.7)	1 (1.7)	1 (1.6)	4 (1.1)
Other	0	0	1 (1.6)	0	0	0	1 (0.3)
Protocol violation	4 (6.7)	2 (3.3)	2 (3.3)	3 (5.0)	1 (1.7)	1 (1.6)	13 (3.6)
Subject request	1 (1.7)	2 (3.3)	3 (4.9)	1 (1.7)	0	3 (4.8)	10 (2.8)
Unsatisfactory response - efficacy	5 (8.3)	2 (3.3)	4 (6.6)	1 (1.7)	4 (6.7)	2 (3.2)	18 (5.0)

BID = twice daily, N = total number of subjects, n = number of subjects per treatment group, QD = once daily.
a. Total discontinued was the sum of individual reasons since they were mutually exclusive by subject.

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Table 3. Summary of Demographic Characteristics

Characteristic	Placebo n=60	Giripladib 50 mg QD n=60	Giripladib 200 mg QD n=61	Giripladib 400 mg QD n=60	Giripladib 200 mg BID n=60	Naproxen 500 mg BID n=62	Total N=363
Age (years)							
Mean	61.43	62.55	60.92	61.82	61.88	61.34	61.65
Standard deviation	6.98	7.66	5.29	6.41	6.44	6.91	6.63
Minimum	50.00	50.00	52.00	51.00	49.00	49.00	49.00
Maximum	75.00	75.00	74.00	74.00	74.00	74.00	75.00
Median	60.50	61.50	60.00	60.50	63.00	60.50	61.00
Sex							
Female	51 (85.00)	44 (73.33)	45 (73.77)	43 (71.67)	45 (75.00)	46 (74.19)	274 (75.48)
Male	9 (15.00)	16 (26.67)	16 (26.23)	17 (28.33)	15 (25.00)	16 (25.81)	89 (24.52)
Race							
American Indian or Alaska Native	0	0	0	1 (1.67)	0	0	1 (0.28)
Asian	1 (1.67)	0	0	0	1 (1.67)	1 (1.61)	3 (0.83)
Black or African American	3 (5.00)	0	1 (1.64)	1 (1.67)	1 (1.67)	2 (3.23)	8 (2.20)
Other	2 (3.33)	5 (8.33)	5 (8.20)	5 (8.33)	4 (6.67)	5 (8.06)	26 (7.16)
White	54 (90.00)	55 (91.67)	55 (90.16)	53 (88.33)	54 (90.00)	54 (87.10)	325 (89.53)
Ethnic origin							
Hispanic or Latino	5 (8.33)	8 (13.33)	9 (14.75)	9 (15.00)	7 (11.67)	8 (12.90)	46 (12.67)
Non-Hispanic and Non-Latino	55 (91.67)	52 (86.67)	52 (85.25)	51 (85.00)	53 (88.33)	54 (87.10)	317 (87.33)

BID = twice daily, n= number of subjects per treatment group, N = total number of subjects, QD = once daily.

Efficacy Results: Two (2) prespecified interim analyses were conducted. The first interim analysis occurred when approximately 25% of planned subjects had completed at least 4 weeks of treatment. This early evaluation was used for administrative purposes to assess efficacy variability among dosing groups. The standard deviation of WOMAC walking pain estimated at the first interim analysis was close to the assumed value, 25 mm.

The second interim efficacy data review was performed after approximately 50% of planned subjects had completed or prematurely withdrawn from the study. The analysis was used to determine whether any of the giripladib treatment groups had an adequate response (improvement over placebo) and whether the response for naproxen compared with placebo provided the expected response in this study. The results of the second interim efficacy analyses are presented in Table 4, Table 5, Table 6, Table 7, Table 8, Table 9 and Table 10.

The mean WOMAC VAS walking pain score at Baseline ranged from 62.4 to 68.1 mm across all treatment groups. There was an improvement in mean WOMAC VAS walking pain score at Week 6 by 36.1 mm (SD=26.5) with naproxen 500 mg BID, by 34.9 mm (SD=30.6) with giripladib 400 mg QD, by 32.2 mm (SD=25.0) with giripladib 200 mg QD, by 27.8 mm (SD=25.4) with giripladib 200 mg BID, by 26.2 mm (SD=27.9) with giripladib 50 mg QD, and by 24.9 mm (SD=25.6) with placebo.

At Week 6, mean WOMAC VAS walking pain score improved by 34.9 to 26.2 mm among subjects treated with giripladib and by 36.1 mm among subjects treated with naproxen 500-mg BID; none of the treatment groups were statistically significantly different from placebo. Giripladib did not meet the prespecified efficacy criteria for continuation of the development program in OA. The final efficacy analyses were not performed as this study was prematurely terminated.

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Table 4. ANCOVA Results for WOMAC Walking Pain MITT With LOCF

			Raw	Raw Change	Adjusted Change	Difference in Adjusted Change vs Placebo		Difference in Adjusted Change Between Giripladib 200 mg BID vs 400 mg QD	
	Treatment	N	Mean (SD)	Mean (SD)	Mean (SE)	Mean (95% CI)	p-Value[a]	Mean (95% CI)	p-Value[a]
Baseline	Placebo	41	64.0 (14.6)						
	Giripladib 50 mg QD	41	65.0 (13.3)						
	Giripladib 200 mg QD	41	68.1 (15.5)						
	Giripladib 400 mg QD	43	65.1 (21.3)						
	Giripladib 200 mg BID	43	62.4 (19.0)						
	Naproxen 500 mg BID	42	64.5 (15.7)						
Week 1	Placebo	41	47.0 (22.8)	-17.0 (22.1)	-17.4 (3.4)				
	Giripladib 50 mg QD	41	46.1 (24.0)	-18.9 (22.4)	-18.8 (3.4)	-1.4 (-10.9,8.0)	0.765		
	Giripladib 200 mg QD	41	48.0 (24.6)	-20.1 (21.6)	-18.9 (3.4)	-1.5 (-11.0,8.0)	0.753		
	Giripladib 400 mg QD	43	41.1 (25.1)	-24.0 (24.2)	-23.9 (3.3)	-6.5 (-15.9,2.8)	0.171		
	Giripladib 200 mg BID	43	42.4 (24.1)	-20.0 (23.9)	-20.9 (3.3)	-3.5 (-12.9,5.8)	0.457	3.0 (-6.3,12.2)	0.526
	Naproxen 500 mg BID	42	42.7 (23.8)	-21.7 (21.4)	-21.9 (3.4)	-4.5 (-13.9,4.9)	0.348		
Week 2	Placebo	41	46.0 (26.6)	-18.0 (26.1)	-18.4 (3.7)				
	Giripladib 50 mg QD	41	45.5 (26.6)	-19.5 (25.5)	-19.4 (3.7)	-1.1 (-11.4,9.2)	0.839		
	Giripladib 200 mg QD	41	41.9 (26.4)	-26.2 (23.7)	-24.9 (3.7)	-6.5 (-16.8,3.9)	0.218		
	Giripladib 400 mg QD	43	39.0 (24.1)	-26.1 (24.3)	-26.0 (3.6)	-7.6 (-17.8,2.5)	0.141		
	Giripladib 200 mg BID	43	38.2 (25.3)	-24.2 (24.1)	-25.2 (3.6)	-6.8 (-17.0,3.4)	0.187	0.8 (-9.3,10.9)	0.876
	Naproxen 500 mg BID	42	36.8 (25.0)	-27.7 (24.1)	-27.8 (3.7)	-9.5 (-19.7,0.8)	0.070		
Week 3	Placebo	41	40.7 (27.6)	-23.3 (25.8)	-23.7 (4.0)				
	Giripladib 50 mg QD	41	41.0 (27.2)	-24.0 (26.0)	-24.0 (4.0)	-0.3 (-11.4,10.8)	0.957		
	Giripladib 200 mg QD	41	40.2 (28.3)	-27.9 (26.0)	-26.4 (4.0)	-2.7 (-13.8,8.4)	0.631		
	Giripladib 400 mg QD	43	39.3 (28.1)	-25.8 (29.3)	-25.6 (3.9)	-2.0 (-12.9,8.9)	0.720		
	Giripladib 200 mg BID	43	35.6 (25.9)	-26.8 (24.7)	-27.9 (3.9)	-4.3 (-15.2,6.7)	0.443	-2.3 (-13.1,8.5)	0.679
	Naproxen 500 mg BID	42	33.7 (24.5)	-30.7 (27.2)	-30.9 (3.9)	-7.3 (-18.3,3.7)	0.195		
Week 4	Placebo	41	41.5 (26.3)	-22.5 (24.2)	-22.9 (4.0)				
	Giripladib 50 mg QD	41	38.8 (27.5)	-26.2 (27.7)	-26.1 (4.0)	-3.2 (-14.2,7.9)	0.575		
	Giripladib 200 mg QD	41	41.0 (28.2)	-27.1 (26.2)	-25.5 (4.0)	-2.6 (-13.7,8.5)	0.646		
	Giripladib 400 mg QD	43	34.8 (29.0)	-30.3 (31.7)	-30.2 (3.9)	-7.2 (-18.2,3.7)	0.195		
	Giripladib 200 mg BID	43	33.4 (24.7)	-29.0 (23.9)	-30.2 (3.9)	-7.2 (-18.2,3.7)	0.196	0.0 (-10.8,10.8)	0.997
	Naproxen 500 mg BID	42	32.8 (24.8)	-31.7(25.8)	-31.9 (3.9)	-8.9 (-19.9,2.1)	0.111		
Week 5	Placebo	41	41.5 (27.8)	-22.5 (26.7)	-22.9 (3.9)				
	Giripladib 50 mg QD	41	39.8 (27.1)	-25.2 (26.8)	-25.1 (3.9)	-2.2 (-13.1,8.7)	0.694		

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Table 4. ANCOVA Results for WOMAC Walking Pain MITT With LOCF

			Raw	Raw Change	Adjusted Change	Difference in Adjusted Change vs Placebo		Difference in Adjusted Change Between Giripladib 200 mg BID vs 400 mg QD	
	Treatment	N	Mean (SD)	Mean (SD)	Mean (SE)	Mean (95% CI)	p-Value[a]	Mean (95% CI)	p-Value[a]
Week 6	Giripladib 200 mg QD	41	38.3(27.6)	-29.8 (25.2)	-28.1 (3.9)	-5.1 (-16.1,5.8)	0.356		
	Giripladib 400 mg QD	43	32.0 (27.4)	-33.2 (28.3)	-33.0 (3.8)	-10.1 (-20.9,0.7)	0.067		
	Giripladib 200 mg BID	43	33.0 (22.8)	-29.4 (23.0)	-30.7 (3.8)	-7.8 (-18.6,3.0)	0.156	2.3 (-8.4,12.9)	0.676
	Naproxen 500 mg BID	42	30.7 (24.4)	-33.7 (29.2)	-33.9 (3.9)	-11.0 (-21.9,-0.2)	0.047		
	Placebo	41	39.1 (27.4)	-24.9 (25.6)	-25.4 (4.0)				
	Giripladib 50 mg QD	41	38.8 (27.4)	-26.2 (27.9)	-26.1 (4.0)	-0.8 (-11.8,10.3)	0.892		
	Giripladib 200 mg QD	41	35.9 (27.8)	-32.2 (25.0)	-30.4 (4.0)	-5.1 (-16.1,6.0)	0.368		
	Giripladib 400 mg QD	43	30.2 (27.3)	-34.9 (30.6)	-34.7 (3.9)	-9.4 (-20.3,1.5)	0.091		
	Giripladib 200 mg BID	43	34.6 (25.1)	-27.8 (25.4)	-29.2 (3.9)	-3.8 (-14.7,7.1)	0.493	5.6 (-5.2,16.4)	0.309
	Naproxen 500 mg BID	42	28.3 (23.5)	-36.1 (26.5)	-36.3 (3.9)	-11.0 (-21.9,-0.0)	0.050		

ANCOVA = analysis of covariance; BID = twice a day; CI = confidence interval; LOCF = last observation carried forward; mITT = modified intent-to-treat; QD = once a day; N = number of subjects; SD = standard deviation; SE = standard error; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.

a. The p-values based on ANCOVA model: change = baseline + treatment.

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Table 5. ANCOVA Results for WOMAC Function Subscale MITT With LOCF

			Raw	Raw Change	Adjusted Change	Difference in Adjusted Change vs Placebo		Difference in Adjusted Change Between Giripladib 200 mg BID vs 400 mg QD	
	Treatment	N	Mean (SD)	Mean (SD)	Mean (SE)	Mean (95% CI)	p-Value[a]	Mean (95% CI)	p-Value[a]
Baseline	Placebo	41	65.2 (16.6)						
	Giripladib 50 mg QD	41	64.9 (16.4)						
	Giripladib 200 mg QD	41	65.9 (19.6)						
	Giripladib 400 mg QD	43	63.7 (18.9)						
	Giripladib 200 mg BID	43	63.0 (17.6)						
	Naproxen 500 mg BID	42	61.8 (20.0)						
Week 1	Placebo	41	49.6 (22.3)	-15.6 (22.0)	-15.3 (2.9)				
	Giripladib 50 mg QD	41	46.2 (22.8)	-18.7 (18.3)	-18.5 (2.9)	-3.2 (-11.4,5.0)	0.440		
	Giripladib 200 mg QD	41	51.8 (23.6)	-14.1 (16.9)	-13.6 (2.9)	1.7 (-6.5,9.8)	0.686		
	Giripladib 400 mg QD	43	43.6 (23.2)	-20.0 (18.4)	-20.1 (2.9)	-4.8 (-12.9,3.2)	0.237		
	Giripladib 200 mg BID	43	44.4 (24.6)	-18.6 (21.4)	-18.9 (2.9)	-3.6 (-11.6,4.5)	0.382	1.3 (-6.7,9.2)	0.754
	Naproxen 500 mg BID	42	44.2 (22.3)	-17.6 (17.9)	-18.1 (2.9)	-2.8 (-11.0,5.3)	0.490		
Week 2	Placebo	41	45.4 (22.3)	-19.7 (21.6)	-19.4 (3.1)				
	Giripladib 50 mg QD	41	44.7 (23.7)	-20.2 (18.8)	-19.9 (3.1)	-0.5 (-9.1,8.1)	0.906		
	Giripladib 200 mg QD	41	45.5 (24.5)	-20.4 (20.3)	-19.9 (3.1)	-0.5 (-9.1,8.1)	0.910		
	Giripladib 400 mg QD	43	42.1 (23.2)	-21.6 (19.3)	-21.7 (3.0)	-2.3 (-10.8,6.2)	0.595		
	Giripladib 200 mg BID	43	40.1 (24.2)	-22.8 (21.1)	-23.1 (3.0)	-3.7 (-12.2,4.8)	0.392	-1.4 (-9.8,7.0)	0.742
	Naproxen 500 mg BID	42	39.6 (24.7)	-22.2 (20.3)	-22.8 (3.0)	-3.4 (-11.9,5.1)	0.434		
Week 3	Placebo	41	42.9 (27.3)	-22.3 (24.3)	-21.9 (3.4)				
	Giripladib 50 mg QD	41	43.7 (23.3)	-21.2 (22.5)	-21.0 (3.4)	1.0 (-8.5,10.5)	0.841		
	Giripladib 200 mg QD	41	46.0 (25.9)	-19.9 (21.4)	-19.3 (3.4)	2.6 (-6.9,12.1)	0.588		
	Giripladib 400 mg QD	43	38.9 (25.5)	-24.8 (23.6)	-24.9 (3.3)	-3.0 (-12.4,6.4)	0.528		
	Giripladib 200 mg BID	43	39.2 (25.1)	-23.8 (21.0)	-24.2 (3.3)	-2.2 (-11.6,7.2)	0.642	0.8 (-8.5,10.1)	0.867
	Naproxen 500 mg BID	42	34.9 (22.9)	-26.9 (22.7)	-27.6 (3.4)	-5.7 (-15.2,3.8)	0.236		
Week 4	Placebo	41	42.7 (26.7)	-22.5 (25.8)	-22.0 (3.5)				
	Giripladib 50 mg QD	41	41.3 (24.4)	-23.6 (23.7)	-23.2 (3.5)	-1.2 (-11.1,8.7)	0.810		
	Giripladib 200 mg QD	41	44.5 (25.5)	-21.4 (21.1)	-20.7 (3.5)	1.4 (-8.5,11.2)	0.783		
	Giripladib 400 mg QD	43	37.6 (25.5)	-26.1 (25.9)	-26.2 (3.5)	-4.2 (-13.9,5.6)	0.400		
	Giripladib 200 mg BID	43	37.5 (24.7)	-25.5 (21.4)	-25.9 (3.5)	-3.8 (-13.6,5.9)	0.439	0.3 (-9.3,10.0)	0.946
	Naproxen 500 mg BID	42	34.5 (24.0)	-27.2 (24.3)	-28.1 (3.5)	-6.1 (-15.9,3.7)	0.221		
Week 5	Placebo	41	43.0 (26.7)	-22.2 (23.5)	-21.7 (3.5)				
	Giripladib 50 mg QD	41	42.1 (24.5)	-22.9 (23.4)	-22.5 (3.5)	-0.8 (-10.6,9.0)	0.877		
	Giripladib 200 mg QD	41	42.4 (25.8)	-23.5 (20.8)	-22.7 (3.5)	-1.0 (-10.8,8.8)	0.839		
	Giripladib 400 mg QD	43	35.2 (25.6)	-28.4 (25.8)	-28.6 (3.4)	-6.9 (-16.6,2.8)	0.165		

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Table 5. ANCOVA Results for WOMAC Function Subscale MITT With LOCF

			Raw	Raw Change	Adjusted Change	Difference in Adjusted Change vs Placebo		Difference in Adjusted Change Between Giripladib 200 mg BID vs 400 mg QD	
	Treatment	N	Mean (SD)	Mean (SD)	Mean (SE)	Mean (95% CI)	p-Value[a]	Mean (95% CI)	p-Value[a]
Week 6	Giripladib 200 mg BID	43	37.1 (23.8)	-25.8 (20.7)	-26.3 (3.4)	-4.5 (-14.2,5.2)	0.358	2.3 (-7.3,11.9)	0.634
	Naproxen 500 mg BID	42	34.0 (23.5)	-27.8 (27.0)	-28.7 (3.5)	-6.9 (-16.7,2.8)	0.163		
	Placebo	41	41.9 (27.2)	-23.2 (24.0)	-22.8 (3.7)				
	Giripladib 50 mg QD	41	43.6 (25.8)	-21.3 (24.1)	-20.9 (3.7)	1.8 (-8.3,12.0)	0.723		
	Giripladib 200 mg QD	41	40.3 (25.7)	-25.5 (20.7)	-24.8 (3.7)	-2.0 (-12.2,8.2)	0.698		
	Giripladib 400 mg QD	43	33.4 (26.1)	-30.3 (27.6)	-30.4 (3.6)	-7.7 (-17.7,2.4)	0.135		
	Giripladib 200 mg BID	43	37.8 (25.2)	-25.1 (22.6)	-25.6 (3.6)	-2.8 (-12.9,7.2)	0.581	4.8 (-5.1,14.8)	0.339
	Naproxen 500 mg BID	42	30.7 (23.7)	-31.1 (27.6)	-32.0 (3.6)	-9.3 (-19.4,0.9)	0.073		

ANCOVA = analysis of covariance; BID = twice a day; CI = confidence interval; LOCF = last observation carried forward; mITT = modified intent-to-treat; QD = once a day; N = number of subjects; SD = standard deviation; SE = standard error; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.

a. The p-values based on ANCOVA model: change = baseline + treatment.

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Table 6. ANCOVA Results for Subject Overall Evaluation MITT With LOCF

			Raw	Raw Change	Adjusted Change	Difference in Adjusted Change vs Placebo		Difference in Adjusted Change Between Giripladib 200 mg BID vs 400 mg QD	
	Treatment	N	Mean (SD)	Mean (SD)	Mean (SE)	Mean (95% CI)	p-Value[a]	Mean (95% CI)	p-Value[a]
Baseline	Placebo	41	4.1 (0.6)						
	Giripladib 50 mg QD	41	4.2 (0.6)						
	Giripladib 200 mg QD	42	4.4 (0.5)						
	Giripladib 400 mg QD	43	4.2 (0.7)						
	Giripladib 200 mg BID	43	4.1 (0.6)						
	Naproxen 500 mg BID	42	4.1 (0.6)						
Week 1	Placebo	41	3.3 (0.8)	-0.8 (0.8)	-0.9 (0.1)				
	Giripladib 50 mg QD	41	3.3 (0.8)	-0.9 (1.1)	-0.9 (0.1)	-0.0 (-0.4,0.4)	0.992		
	Giripladib 200 mg QD	42	3.3 (0.9)	-1.1 (1.1)	-0.9 (0.1)	-0.1 (-0.4,0.3)	0.696		
	Giripladib 400 mg QD	43	2.8 (0.8)	-1.4 (0.8)	-1.4 (0.1)	-0.5 (-0.8,-0.1)	0.007		
	Giripladib 200 mg BID	43	3.1 (0.9)	-1.0 (1.0)	-1.0 (0.1)	-0.2 (-0.5,0.2)	0.405	0.3 (-0.0,0.7)	0.059
	Naproxen 500 mg BID	42	3.1 (0.8)	-0.9 (0.8)	-1.0 (0.1)	-0.1 (-0.5,0.2)	0.493		
Week 2	Placebo	41	3.0 (0.8)	-1.0 (0.9)	-1.1 (0.1)				
	Giripladib 50 mg QD	41	3.2 (0.9)	-1.0 (1.1)	-0.9 (0.1)	0.2 (-0.2,0.5)	0.358		
	Giripladib 200 mg QD	42	3.2 (0.9)	-1.2 (0.9)	-1.1 (0.1)	0.0 (-0.3,0.4)	0.861		
	Giripladib 400 mg QD	43	3.1 (0.8)	-1.1 (0.7)	-1.1 (0.1)	0.0 (-0.3,0.4)	0.895		
	Giripladib 200 mg BID	43	3.0 (0.9)	-1.1 (0.9)	-1.2 (0.1)	-0.1 (-0.4,0.3)	0.689	-0.1 (-0.4,0.2)	0.591
	Naproxen 500 mg BID	42	2.9 (0.8)	-1.2 (0.8)	-1.3 (0.1)	-0.2 (-0.5,0.2)	0.342		
Week 3	Placebo	41	3.0 (1.0)	-1.1 (1.1)	-1.2 (0.1)				
	Giripladib 50 mg QD	41	3.3 (0.7)	-0.9 (1.0)	-0.9 (0.1)	0.3 (-0.1,0.7)	0.101		
	Giripladib 200 mg QD	42	3.1 (1.0))	-1.3 (1.0)	-1.1 (0.1)	0.1 (-0.3,0.4)	0.792		
	Giripladib 400 mg QD	43	2.9 (0.8)	-1.3 (0.9)	-1.3 (0.1)	-0.1 (-0.5,0.3)	0.662		
	Giripladib 200 mg BID	43	2.8 (0.9)	-1.2 (0.9)	-1.3 (0.1)	-0.1 (-0.5,0.3)	0.548	-0.0 (-0.4,0.3)	0.870
	Naproxen 500 mg BID	42	2.8 (0.8)	-1.2 (0.8)	-1.3 (0.1)	-0.1 (-0.5,0.3)	0.535		
Week 4	Placebo	41	2.9 (1.1)	-1.2 (1.2)	-1.2 (0.1)				
	Giripladib 50 mg QD	41	3.2 (0.8)	-1.0 (1.1)	-1.0 (0.1)	0.2 (-0.2,0.6)	0.232		
	Giripladib 200 mg QD	42	3.0 (0.9)	-1.4 (1.0)	-1.2 (0.1)	0.0 (-0.4,0.4)	0.892		
	Giripladib 400 mg QD	43	2.8 (0.8)	-1.4 (0.9)	-1.4 (0.1)	-0.2 (-0.5,0.2)	0.450		
	Giripladib 200 mg BID	43	2.9 (1.0)	-1.1 (1.1)	-1.2 (0.1)	0.0 (-0.4,0.4)	0.885	0.2 (-0.2,0.6)	0.362
	Naproxen 500 mg BID	42	2.8 (0.8)	-1.3 (0.8)	-1.4 (0.1)	-0.1 (-0.5,0.3)	0.560		
Week 5	Placebo	41	2.9 (1.0)	-1.1 (1.1)	-1.2 (0.1)				
	Giripladib 50 mg QD	41	3.1 (0.9)	-1.0 (1.2)	-1.0 (0.1)	0.2 (-0.2,0.6)	0.425		
	Giripladib 200 mg QD	42	2.9 (0.9)	-1.5 (0.9)	-1.3 (0.1)	-0.1 (-0.5,0.3)	0.526		
	Giripladib 400 mg QD	43	2.7 (0.9)	-1.6 (0.9)	-1.5 (0.1)	-0.3 (-0.7,0.1)	0.115		

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Table 6. ANCOVA Results for Subject Overall Evaluation MITT With LOCF

			Raw	Raw Change	Adjusted Change	Difference in Adjusted Change vs Placebo		Difference in Adjusted Change Between Giripladib 200 mg BID vs 400 mg QD	
	Treatment	N	Mean (SD)	Mean (SD)	Mean (SE)	Mean (95% CI)	p-Value[a]	Mean (95% CI)	p-Value[a]
Week 6	Giripladib 200 mg BID	43	2.9 (1.0)	-1.1 (1.0)	-1.2 (0.1)	0.0 (-0.4,0.4)	0.982	0.3 (-0.1,0.7)	0.105
	Naproxen 500 mg BID	42	2.6 (1.0)	-1.5 (0.9)	-1.5 (0.1)	-0.3 (-0.7,0.1)	0.131		
	Placebo	41	2.9 (1.0)	-1.2 (1.1)	-1.2 (0.2)				
	Giripladib 50 mg QD	41	3.1 (0.9)	-1.0 (1.2)	-1.0 (0.2)	0.2 (-0.2,0.6)	0.338		
	Giripladib 200 mg QD	42	2.9 (1.0)	-1.5 (1.0)	-1.4 (0.2)	-0.1 (-0.6,0.3)	0.535		
	Giripladib 400 mg QD	43	2.6 (1.0)	-1.6 (0.9)	-1.6 (0.1)	-0.3 (-0.7,0.1)	0.118		
	PF-05236981 200 mg BID	43	2.9 (1.1)	-1.2 (1.0)	-1.3 (0.1)	-0.0 (-0.5,0.4)	0.847	0.3 (-0.1,0.7)	0.165
	Naproxen 500 mg BID	42	2.5 (1.0)	-1.5 (1.0)	-1.6 (0.1)	-0.4 (-0.8,0.0)	0.075		

ANCOVA = analysis of covariance; BID = twice a day; CI = confidence interval; LOCF = last observation carried forward; mITT = modified intent-to-treat; QD = once a day; N = number of subjects; SD = standard deviation; SE = standard error; vs = versus; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.

a. The p-values based on ANCOVA model: change = baseline + treatment.

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Table 7. ANCOVA Results for Investigator Overall Evaluation MITT With LOCF

			Raw	Raw Change	Adjusted Change	Difference in Adjusted Change vs Placebo		Difference in Adjusted Change Between Giripladib 200 mg BID vs 400 mg QD	
	Treatment	N	Mean (SD)	Mean (SD)	Mean (SE)	Mean (95% CI)	p-Value[a]	Mean (95% CI)	p-Value[a]
Baseline	Placebo	41	4.0 (0.7)						
	Giripladib 50 mg QD	41	4.0 (0.7)						
	Giripladib 200 mg QD	42	4.1 (0.7)						
	Giripladib 400 mg QD	43	4.0 (0.7)						
	Giripladib 200 mg BID	43	4.0 (0.8)						
	Naproxen 500 mg BID	42	3.9 (0.7)						
Week 1	Placebo	41	2.9 (0.9)	-1.0 (0.9)	-1.0 (0.1)				
	Giripladib 50 mg QD	41	3.1 (0.9)	-1.0 (0.9)	-0.9 (0.1)	0.1 (-0.2,0.5)	0.513		
	Giripladib 200 mg QD	42	3.1 (0.9)	-1.0 (1.0)	-0.9 (0.1)	0.1 (-0.3,0.5)	0.556		
	Giripladib 400 mg QD	43	2.6 (0.8)	-1.3 (0.9)	-1.3 (0.1)	-0.3 (-0.7,0.1)	0.098		
	Giripladib 200 mg BID	43	3.0 (0.8)	-1.0 (0.9)	-1.0 (0.1)	0.0 (-0.3,0.4)	0.896	0.3 (-0.0,0.7)	0.071
	Naproxen 500 mg BID	42	2.8 (0.9)	-1.1 (1.0)	-1.2 (0.1)	-0.1 (-0.5,0.3)	0.557		
Week 2	Placebo	41	2.8 (0.9)	-1.1 (1.0)	-1.1 (0.1)				
	Giripladib 50 mg QD	41	2.9 (0.8)	-1.1 (0.9)	-1.1 (0.1)	0.1 (-0.3,0.4)	0.701		
	Giripladib 200 mg QD	42	2.8 (1.0)	-1.3 (1.0)	-1.2 (0.1)	-0.1 (-0.4,0.3)	0.672		
	Giripladib 400 mg QD	43	2.8 (0.8)	-1.2 (1.0)	-1.2 (0.1)	-0.1 (-0.4,0.3)	0.735		
	Giripladib 200 mg BID	43	2.8 (0.9)	-1.2 (1.0)	-1.2 (0.1)	-0.1 (-0.4,0.3)	0.729	-0.0 (-0.4,0.4)	0.994
	Naproxen 500 mg BID	42	2.5 (0.8)	-1.3 (0.9)	-1.4 (0.1)	-0.2 (-0.6,0.1)	0.182		
Week 3	Placebo	41	2.6 (0.9)	-1.3 (1.0)	-1.3 (0.1)				
	Giripladib 50 mg QD	41	2.8 (0.8)	-1.2 (1.0)	-1.2 (0.1)	0.2 (-0.2,0.6)	0.346		
	Giripladib 200 mg QD	42	2.8 (1.0)	-1.3 (1.1)	-1.2 (0.1)	0.1 (-0.2,0.5)	0.466		0.357
	Giripladib 400 mg QD	43	2.5 (0.8)	-1.4 (1.0)	-1.4 (0.1)	-0.1 (-0.5,0.3)	0.594		
	Giripladib 200 mg BID	43	2.7 (0.9)	-1.3 (1.1)	-1.3 (0.1)	0.1 (-0.3,0.4)	0.706	0.2 (-0.2,0.5)	
	Naproxen 500 mg BID	42	2.3 (0.7)	-1.6 (0.9)	-1.7 (0.1)	-0.3 (-0.7,0.0)	0.083		
Week 4	Placebo	41	2.7 (0.9)	-1.2 (1.2)	-1.3 (0.1)				
	Giripladib 50 mg QD	41	2.8 (0.8)	-1.2 (1.0)	-1.2 (0.1)	0.1 (-0.3,0.5)	0.701		
	Giripladib 200 mg QD	42	2.8 (1.2)	-1.3 (1.2)	-1.2 (0.1)	0.1 (-0.3,0.5)	0.681		
	Giripladib 400 mg QD	43	2.4 (0.9)	-1.5 (0.9)	-1.6 (0.1)	-0.3 (-0.7,0.1)	0.158		
	Giripladib 200 mg BID	43	2.7 (1.1)	-1.3 (1.2)	-1.3 (0.1)	-0.0 (-0.4,0.4)	0.894	0.3 (-0.1,0.7)	0.196
	Naproxen 500 mg BID	42	2.4 (0.8)	-1.5 (0.9)	-1.6 (0.1)	-0.3 (-0.7,0.1)	0.142		
Week 5	Placebo	41	2.7 (0.8)	-1.3 (1.1)	-1.3 (0.1)				
	Giripladib 50 mg QD	41	2.6 (0.9)	-1.4 (1.0)	-1.4 (0.1)	-0.0 (-0.4,0.3)	0.830		
	Giripladib 200 mg QD	42	2.6 (1.1)	-1.5 (1.2)	-1.4 (0.1)	-0.1 (-0.5,0.3)	0.514		
	Giripladib 400 mg QD	43	2.4 (0.9)	-1.5 (0.9)	-1.6 (0.1)	-0.2 (-0.6,0.1)	0.220		

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Table 7. ANCOVA Results for Investigator Overall Evaluation MITT With LOCF

			Raw	Raw Change	Adjusted Change	Difference in Adjusted Change vs Placebo		Difference in Adjusted Change Between Giripladib 200 mg BID vs 400 mg QD	
	Treatment	N	Mean (SD)	Mean (SD)	Mean (SE)	Mean (95% CI)	p-Value[a]	Mean (95% CI)	p-Value[a]
Week 6	Giripladib 200 mg BID	43	2.7 (1.0)	-1.3 (1.1)	-1.3 (0.1)	0.0 (-0.4,0.4)	0.914	0.3 (-0.1,0.6)	0.177
	Naproxen 500 mg BID	42	2.4 (0.9)	-1.5 (1.0)	-1.6 (0.1)	-0.3 (-0.6,0.1)	0.198		
	Placebo	41	2.7 (0.9)	-1.3 (1.2)	-1.3 (0.1)				
	Giripladib 50 mg QD	41	2.7 (0.9)	-1.3 (1.1)	-1.3 (0.1)	0.0 (-0.4,0.5)	0.856		
	Giripladib 200 mg QD	42	2.6 (1.1)	-1.5 (1.2)	-1.4 (0.1)	-0.1 (-0.5,0.3)	0.592		
	Giripladib 400 mg QD	43	2.4 (0.9)	-1.6 (1.0)	-1.6 (0.1)	-0.3 (-0.7,0.1)	0.204		
	Giripladib 200 mg BID	43	2.7 (1.0)	-1.3 (1.2)	-1.3 (0.1)	0.1 (-0.4,0.5)	0.803	0.3 (-0.1,0.7)	0.124
	Naproxen 500 mg BID	42	2.4 (0.9)	-1.5 (1.1)	-1.6 (0.1)	-0.3 (-0.7,0.1)	0.169		

ANCOVA = analysis of covariance; BID = twice a day; CI = confidence interval; LOCF = last observation carried forward; mITT = modified intent-to-treat; QD = once a day; N = number of subjects; SD = standard deviation; SE = standard error; vs = versus; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.

a. The p-values based on ANCOVA model: change = baseline + treatment.

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Table 8. ANCOVA Results for WOMAC Pain Subscale MITT With LOCF

			Raw	Raw Change	Adjusted Change	Difference in Adjusted Change vs Placebo		Difference in Adjusted Change Between Giripladib 200 mg BID vs 400 mg QD	
	Treatment	N	Mean (SD)	Mean (SD)	Mean (SE)	Mean (95% CI)	p-Value[a]	Mean (95% CI)	p-Value[a]
Baseline	Placebo	41	63.7 (13.0)						
	Giripladib 50 mg QD	41	62.2 (15.7)						
	Giripladib 200 mg QD	41	66.5 (15.7)						
	Giripladib 400 mg QD	43	61.5 (18.8)						
	Giripladib 200 mg BID	43	62.5 (17.6)						
	Naproxen 500 mg BID	42	62.4 (16.7)						
Week 1	Placebo	41	46.6 (21.1)	-17.1 (18.6)	-17.0 (2.9)				
	Giripladib 50 mg QD	41	43.7 (22.6)	-18.4 (19.4)	-18.7 (2.9)	-1.7 (-9.9,6.4)	0.676		
	Giripladib 200 mg QD	41	49.6 (21.3)	-16.9 (17.3)	-15.9 (2.9)	1.0 (-7.1,9.2)	0.802		
	Giripladib 400 mg QD	43	42.4 (22.0)	-19.1 (19.2)	-19.6 (2.9)	-2.6 (-10.7,5.5)	0.524		
	Giripladib 200 mg BID	43	43.2 (22.8)	-19.2 (22.3)	-19.4 (2.9)	-2.5 (-10.5,5.6)	0.550	0.2 (-7.8,8.1)	0.968
	Naproxen 500 mg BID	42	42.4 (22.6)	-20.0 (18.2)	-20.2 (2.9)	-3.2 (-11.3,4.9)	0.435		
Week 2	Placebo	41	44.7 (23.5)	-19.0 (19.5)	-18.9 (3.1)				
	Giripladib 50 mg QD	41	42.2 (22.7)	-20.0 (19.1)	-20.3 (3.1)	-1.4 (-10.0,7.2)	0.751		
	Giripladib 200 mg QD	41	43.5 (23.8)	-23.0 (21.8)	-22.1 (3.1)	-3.3 (-11.9,5.4)	0.455		
	Giripladib 400 mg QD	43	40.3 (22.3)	-21.3 (20.6)	-21.7 (3.0)	-2.8 (-11.3,5.7)	0.519		
	Giripladib 200 mg BID	43	39.0 (23.4)	-23.5 (20.4)	-23.6 (3.0)	-4.8 (-13.3,3.8)	0.272	-2.0 (-10.4,6.5)	0.646
	Naproxen 500 mg BID	42	36.9 (23.9)	-25.5 (19.7)	-25.7 (3.1)	-6.8 (-15.4,1.8)	0.118		
Week 3	Placebo	41	42.0 (27.3)	-21.8 (23.0)	-21.6 (3.5)				
	Giripladib 50 mg QD	41	41.2 (23.4)	-20.9 (23.2)	-21.2 (3.5)	0.3 (-9.5,10.1)	0.949		
	Giripladib 200 mg QD	41	42.8 (26.3)	-23.7 (23.5)	-22.6 (3.5)	-1.0 (-10.8,8.7)	0.833		
	Giripladib 400 mg QD	43	38.0 (24.9)	-23.5 (24.3)	-24.0 (3.4)	-2.4 (-12.1,7.2)	0.618		
	Giripladib 200 mg BID	43	37.4 (25.1)	-25.1 (21.2)	-25.3 (3.4)	-3.7 (-13.4,5.9)	0.449	-1.3 (-10.8,8.3)	0.793
	Naproxen 500 mg BID	42	33.3 (23.2)	-29.1 (22.9)	-29.3 (3.5)	-7.8 (-17.5,2.0)	0.117		
Week 4	Placebo	41	42.3 (26.2)	-21.4 (23.3)	-21.2 (3.5)				
	Giripladib 50 mg QD	41	40.1 (24.0)	-22.1 (23.6)	-22.5 (3.5)	-1.3 (-11.0,8.5)	0.797		
	Giripladib 200 mg QD	41	41.5 (24.8)	-25.0 (22.1)	-23.8 (3.5)	-2.6 (-12.4,7.1)	0.597		
	Giripladib 400 mg QD	43	34.6 (25.0)	-26.9 (26.2)	-27.5 (3.4)	-6.3 (-15.9,3.4)	0.201		
	Giripladib 200 mg BID	43	35.4 (24.0)	-27.1 (21.0)	-27.3 (3.4)	-6.2 (-15.8,3.5)	0.210	0.1 (-9.4,9.7)	0.979
	Naproxen 500 mg BID	42	32.0 (24.3)	-30.4 (22.3)	-30.7 (3.5)	-9.5 (-19.2,0.2)	0.055		
Week 5	Placebo	41	42.0 (26.1)	-21.8 (22.4)	-21.5 (3.5)				
	Giripladib 50 mg QD	41	39.5 (24.4)	-22.7 (23.7)	-23.1 (3.5)	-1.5 (-11.3, 8.2)	0.757		
	Giripladib 200 mg QD	41	39.1 (25.2)	-27.4 (21.9)	-26.1 (3.5)	-4.5 (-14.3,5.2)	0.362		
	Giripladib 400 mg QD	43	32.2 (24.6)	-29.4 (25.7)	-30.0 (3.4)	-8.5 (-18.1,1.2)	0.085		

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Table 8. ANCOVA Results for WOMAC Pain Subscale MITT With LOCF

			Raw	Raw Change	Adjusted Change	Difference in Adjusted Change vs Placebo		Difference in Adjusted Change Between Giripladib 200 mg BID vs 400 mg QD	
	Treatment	N	Mean (SD)	Mean (SD)	Mean (SE)	Mean (95% CI)	p-Value[a]	Mean (95% CI)	p-Value[a]
Week 6	Giripladib 200 mg BID	43	35.6 (23.0)	-26.9 (19.9)	-27.1 (3.4)	-5.6 (-15.2,4.1)	0.255	2.9 (-6.6,12.4)	0.551
	Naproxen 500 mg BID	42	30.7 (23.3)	-31.7 (25.5)	-32.0 (3.5)	-10.5 (-20.2,-0.8)	0.035		
	Placebo	41	40.1 (27.0)	-23.6 (22.8)	-23.4 (3.6)				
	Giripladib 50 mg QD	41	41.2 (26.3)	-21.0 (25.8)	-21.4 (3.6)	2.0 (-8.2,12.1)	0.704		
	Giripladib 200 mg QD	41	36.4 (24.3)	-30.1 (21.0)	-28.8 (3.7)	-5.4 (-15.6,4.7)	0.294		
	Giripladib 400 mg QD	43	30.1 (24.9)	-31.5 (27.0)	-32.1 (3.6)	-8.7 (-18.8,1.3)	0.087		
	Giripladib 200 mg BID	43	37.7 (25.6)	-24.8 (22.6)	-25.0 (3.6)	-1.7 (-11.7,8.4)	0.744	7.1 (-2.8,17.0)	0.160
	Naproxen 500 mg BID	42	27.8 (23.4)	-34.7 (25.1)	-34.9 (3.6)	-11.6 (-21.7,-1.5)	0.025		

ANCOVA = analysis of covariance; BID = twice a day; CI = confidence interval; LOCF = last observation carried forward; mITT = modified intent-to-treat; N = number of subjects; QD = once a day; SD = standard deviation; SE = standard error; vs = versus; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.

a. The p-values based on ANCOVA model: change = baseline + treatment.

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Table 9. ANCOVA Results for WOMAC Stiffness Subscale MITT With LOCF

			Raw	Raw Change	Adjusted Change	Difference in Adjusted Change vs Placebo		Difference in Adjusted Change Between Giripladib 200 mg BID vs 400 mg QD	
	Treatment	N	Mean (SD)	Mean (SD)	Mean (SE)	Mean (95% CI)	p-Value[a]	Mean (95% CI)	p-Value[a]
Baseline	Placebo	41	70.9 (15.1)						
	Giripladib 50 mg QD	41	63.1 (22.2)						
	Giripladib 200 mg QD	41	67.8 (22.8)						
	Giripladib 400 mg QD	43	64.7 (20.0)						
	Giripladib 200 mg BID	43	65.8 (18.8)						
	Naproxen 500 mg BID	42	62.8 (22.1)						
Week 1	Placebo	41	52.4 (24.1)	-18.6 (23.4)	-16.4 (3.3)				
	Giripladib 50 mg QD	41	46.3 (24.2)	-16.8 (23.3)	-17.9 (3.3)	-1.5 (-10.6,7.7)	0.751		
	Giripladib 200 mg QD	41	52.6 (24.7)	-15.2 (20.7)	-14.4 (3.3)	2.0 (-7.1,11.2)	0.658		
	Giripladib 400 mg QD	43	45.4 (23.6)	-19.3 (22.0)	-19.7 (3.2)	-3.3 (-12.3,5.7)	0.471		
	Giripladib 200 mg BID	43	44.3 (23.9)	-21.5 (23.3)	-21.5 (3.2)	-5.1 (-14.1,3.9)	0.266	-1.8 (-10.7,7.1)	0.691
	Naproxen 500 mg BID	42	42.8 (23.6)	-20.0 (22.5)	-21.3 (3.2)	-4.8 (-13.9,4.3)	0.298		
Week 2	Placebo	41	48.6 (24.4)	-22.4 (23.7)	-20.4 (3.5)				
	Giripladib 50 mg QD	41	44.7 (24.2)	-18.4 (24.4)	-19.5 (3.5)	0.9 (-8.7,10.6)	0.852		
	Giripladib 200 mg QD	41	47.6 (26.3)	-20.1 (23.7)	-19.4 (3.4)	1.0 (-8.6,10.6)	0.840		
	Giripladib 400 mg QD	43	44.0 (24.3)	-20.6 (22.7)	-21.1 (3.4)	-0.7 (-10.2,8.8)	0.883		
	Giripladib 200 mg BID	43	41.7 (25.9)	-24.1 (23.8)	-24.1 (3.4)	-3.7 (-13.3,5.8)	0.439	-3.0 (-12.4,6.3)	0.525
	Naproxen 500 mg BID	42	38.9 (26.4)	-23.8 (22.1)	-25.0 (3.4)	-4.7 (-14.3,5.0)	0.341		
Week 3	Placebo	41	44.2 (28.8)	-26.7 (27.1)	-24.5 (3.8)				
	Giripladib 50 mg QD	41	45.2 (25.1)	-17.9 (26.0)	-19.1 (3.7)	5.4 (-5.1,15.8)	0.315		
	Giripladib 200 mg QD	41	45.8 (26.0)	-22.0 (21.9)	-21.1 (3.7)	3.4 (-7.1,13.8)	0.527		
	Giripladib 400 mg QD	43	39.9 (26.6)	-24.8 (27.6)	-25.3 (3.7)	-0.8 (-11.2,9.5)	0.873		
	Giripladib 200 mg BID	43	36.7 (25.9)	-29.2 (23.0)	-29.2 (3.7)	-4.7 (-15.0,5.6)	0.369	-3.9 (-14.1,6.3)	0.454
	Naproxen 500 mg BID	42	34.6 (26.2)	-28.2 (27.1)	-29.6 (3.7)	-5.1 (-15.5,5.3)	0.336		
Week 4	Placebo	41	43.2 (27.2)	-27.8 (26.7)	-25.3 (3.8)				
	Giripladib 50 mg QD	41	41.0 (26.6)	-22.1 (27.8)	-23.4 (3.8)	1.8 (-8.9,12.6)	0.735		
	Giripladib 200 mg QD	41	45.7 (25.6)	-22.1 (21.5)	-21.1 (3.8)	4.1 (-6.5,14.8)	0.446		
	Giripladib 400 mg QD	43	35.5 (26.4)	-29.2 (30.8)	-29.8 (3.7)	-4.5 (-15.1,6.1)	0.401		
	Giripladib 200 mg BID	43	36.8 (26.1)	-29.0 (22.3)	-29.0 (3.7)	-3.7 (-14.3,6.8)	0.487	0.8 (-9.6,11.2)	0.882
	Naproxen 500 mg BID	42	33.9 (27.3)	-28.9 (28.1)	-30.4 (3.8)	-5.1 (-15.8,5.6)	0.347		
Week 5	Placebo	41	43.2 (25.5)	-27.8 (24.4)	-25.2 (3.8)				
	Giripladib 50 mg QD	41	42.7 (26.6)	-20.4 (27.1)	-21.7 (3.8)	3.5 (-7.2,14.1)	0.520		
	Giripladib 200 mg QD	41	40.9 (28.1)	-26.9 (24.6)	-26.0 (3.8)	-0.7 (-11.3,9.9)	0.892		
	Giripladib 400 mg QD	43	32.8 (26.6)	-31.9 (28.6)	-32.4 (3.7)	-7.2 (-17.7,3.3)	0.177		

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Table 9. ANCOVA Results for WOMAC Stiffness Subscale MITT With LOCF

			Raw	Raw Change	Adjusted Change	Difference in Adjusted Change vs Placebo		Difference in Adjusted Change Between Giripladib 200 mg BID vs 400 mg QD	
	Treatment	N	Mean (SD)	Mean (SD)	Mean (SE)	Mean (95% CI)	p-Value[a]	Mean (95% CI)	p-Value[a]
Week 6	Giripladib 200 mg BID	43	37.7 (24.8)	-28.2 (21.7)	-28.1 (3.7)	-2.9 (-13.4,7.6)	0.583	4.3 (-6.0,14.6)	0.414
	Naproxen 500 mg BID	42	31.9 (26.5)	-30.8 (30.3)	-32.4 (3.8)	-7.1 (-17.7,3.4)	0.186		
	Placebo	41	41.5 (27.0)	-29.5 (26.1)	-27.1 (3.9)				
	Giripladib 50 mg QD	41	43.9 (28.6)	-19.2 (27.4)	-20.5 (3.9)	6.6 (-4.4,17.6)	0.236		
	Giripladib 200 mg QD	41	38.3 (26.6)	-29.5 (22.2)	-28.6 (3.9)	-1.5 (-12.4,9.5)	0.794		
	Giripladib 400 mg QD	43	32.1 (27.1)	-32.6 (29.5)	-33.2 (3.8)	-6.0 (-16.9,4.8)	0.273		
	Giripladib 200 mg BID	43	37.6 (28.0)	-28.3 (25.1)	-28.3 (3.8)	-1.2 (-12.0,9.6)	0.832	4.9 (-5.8,15.5)	0.369
	Naproxen 500 mg BID	42	29.7 (26.3)	-33.0 (29.4)	-34.5 (3.9)	-7.4 (-18.3,3.6)	0.186		

ANCOVA = analysis of covariance; BID = twice a day; CI = confidence interval; LOCF = last observation carried forward; mITT = modified intent-to-treat; N = number of subjects; QD = once a day; SD = standard deviation; SE = standard error; vs = versus; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.

a. The p-values based on ANCOVA model: change = baseline + treatment.

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Table 10. ANCOVA Results for WOMAC Composite Score MITT With LOCF

			Raw	Raw Change	Adjusted Change	Difference in Adjusted Change vs Placebo		Difference in Adjusted Change Between Giripladib 200 mg BID vs 400 mg QD	
	Treatment	N	Mean (SD)	Mean (SD)	Mean (SE)	Mean (95% CI)	p-Value[a]	Mean (95% CI)	p-Value[a]
Baseline	Placebo	41	65.4 (14.8)						
	Giripladib 50 mg QD	41	64.2 (16.0)						
	Giripladib 200 mg QD	41	66.2 (18.2)						
	Giripladib 400 mg QD	43	63.3 (18.3)						
	Giripladib 200 mg BID	43	63.1 (17.3)						
	Naproxen 500 mg BID	42	62.0 (18.7)						
Week 1	Placebo	41	49.2 (21.7)	-16.1 (20.7)	-15.8 (2.9)				
	Giripladib 50 mg QD	41	45.7 (22.3)	-18.5 (18.2)	-18.4 (2.9)	-2.6 (-10.6,5.4)	0.519		
	Giripladib 200 mg QD	41	51.4 (22.8)	-14.8 (16.4)	-14.2 (2.9)	1.6 (-6.4,9.6)	0.695		
	Giripladib 400 mg QD	43	43.5 (22.6)	-19.8 (18.1)	-20.0 (2.8)	-4.1 (-12.0,3.8)	0.305		
	Giripladib 200 mg BID	43	44.1 (23.8)	-19.0 (21.3)	-19.2 (2.8)	-3.4 (-11.3,4.5)	0.402	0.8 (-7.0,8.6)	0.848
	Naproxen 500 mg BID	42	43.7 (22.1)	-18.3 (17.4)	-18.7 (2.8)	-2.9 (-10.9,5.0)	0.470		
Week 2	Placebo	41	45.6 (22.1)	-19.8 (20.6)	-19.5 (3.0)				
	Giripladib 50 mg QD	41	44.2 (23.0)	-20.0 (18.4)	-19.9 (3.0)	-0.5 (-8.9,8.0)	0.913		
	Giripladib 200 mg QD	41	45.2 (24.0)	-20.9 (20.0)	-20.4 (3.0)	-0.9 (-9.3,7.5)	0.827		
	Giripladib 400 mg QD	43	41.9 (22.8)	-21.5 (19.0)	-21.6 (3.0)	-2.1 (-10.5,6.2)	0.612		
	Giripladib 200 mg BID	43	40.0 (23.8)	-23.1 (20.7)	-23.3 (3.0)	-3.8 (-12.1,4.5)	0.369	-1.7 (-9.9,6.6)	0.691
	Naproxen 500 mg BID	42	39.0 (24.4)	-23.0 (19.6)	-23.5 (3.0)	-4.0 (-12.4,4.3)	0.344		
Week 3	Placebo	41	42.8 (27.2)	-22.6 (23.8)	-22.1 (3.4)				
	Giripladib 50 mg QD	41	43.3 (23.0)	-20.9 (22.5)	-20.8 (3.4)	1.3 (-8.2,10.8)	0.786		
	Giripladib 200 mg QD	41	45.3 (25.4)	-20.9 (21.1)	-20.2 (3.4)	1.9 (-7.5,11.4)	0.687		
	Giripladib 400 mg QD	43	38.8 (25.2)	-24.6 (23.4)	-24.8 (3.3)	-2.6 (-12.0,6.7)	0.582		
	Giripladib 200 mg BID	43	38.6 (25.0)	-24.5 (20.7)	-24.8 (3.3)	-2.6 (-12.0,6.7)	0.578	-0.0 (-9.3,9.2)	0.995
	Naproxen 500 mg BID	42	34.5 (22.8)	-27.5 (22.3)	-28.1 (3.4)	-5.9 (-15.3,3.5)	0.216		
Week 4	Placebo	41	42.7 (26.4)	-22.7 (24.8)	-22.2 (3.5)				
	Giripladib 50 mg QD	41	41.0 (24.0)	-23.2 (23.4)	-23.1 (3.5)	-0.9 (-10.6,8.8)	0.858		
	Giripladib 200 mg QD	41	44.0 (24.9)	-22.2 (20.6)	-21.4 (3.5)	0.8 (-8.9,10.5)	0.872		
	Giripladib 400 mg QD	43	36.8 (25.1)	-26.5 (25.5)	-26.8 (3.4)	-4.6 (-14.2,5.1)	0.352		
	Giripladib 200 mg BID	43	37.0 (24.5)	-26.1 (20.9)	-26.4 (3.4)	-4.2 (-13.8,5.4)	0.388	0.3 (-9.2,9.8)	0.945
	Naproxen 500 mg BID	42	34.0 (24.0)	-28.0 (23.5)	-28.8 (3.5)	-6.6 (-16.3,3.1)	0.181		
Week 5	Placebo	41	42.8 (26.2)	-22.6 (22.8)	-22.1 (3.5)				
	Giripladib 50 mg QD	41	41.6 (24.3)	-22.6 (23.3)	-22.5 (3.5)	-0.5 (-10.2,9.2)	0.920		
	Giripladib 200 mg QD	41	41.6 (25.5)	-24.6 (20.6)	-23.8 (3.5)	-1.7 (-11.4,8.0)	0.728		
	Giripladib 400 mg QD	43	34.4 (25.0)	-28.9 (25.0)	-29.2 (3.4)	-7.1 (-16.7,2.4)	0.143		

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Table 10. ANCOVA Results for WOMAC Composite Score MITT With LOCF

			Raw	Raw Change	Adjusted Change	Difference in Adjusted Change vs Placebo		Difference in Adjusted Change Between Giripladib 200 mg BID vs 400 mg QD	
	Treatment	N	Mean (SD)	Mean (SD)	Mean (SE)	Mean (95% CI)	p-Value[a]	Mean (95% CI)	p-Value[a]
Week 6	Giripladib 200 mg BID	43	36.9 (23.5)	-26.2 (20.2)	-26.6 (3.4)	-4.5 (-14.1,5.0)	0.351	2.6 (-6.9,12.0)	0.589
	Naproxen 500 mg BID	42	33.2 (23.4)	-28.8 (26.4)	-29.6 (3.4)	-7.6 (-17.2,2.1)	0.124		
	Placebo	41	41.5 (26.9)	-23.8 (23.3)	-23.3 (3.6)				
	Giripladib 50 mg QD	41	43.1 (25.6)	-21.1 (24.2)	-21.0 (3.6)	2.3 (-7.7,12.4)	0.651		
	Giripladib 200 mg QD	41	39.3 (25.2)	-26.8 (20.0)	-26.0 (3.6)	-2.7 (-12.7,7.4)	0.601		
	Giripladib 400 mg QD	43	32.6 (25.5)	-30.7 (26.8)	-31.0 (3.5)	-7.7 (-17.6,2.3)	0.129		
	Giripladib 200 mg BID	43	37.8 (25.2)	-25.3 (22.5)	-25.7 (3.5)	-2.4 (-12.3,7.6)	0.640	5.3 (-4.5,15.1)	0.287
	Naproxen 500 mg BID	42	30.0 (23.6)	-32.0 (26.7)	-32.8 (3.6)	-9.5 (-19.5,0.5)	0.063		

ANCOVA = analysis of covariance; BID = twice a day; CI = confidence interval; LOCF = last observation carried forward; mITT = modified intent-to-treat; N = number of subjects; QD = once a day; SD = standard deviation; SE = standard error; vs = versus; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.

a. The p-values based on ANCOVA model: change = baseline + treatment.

Safety Results: A total of 257 subjects had reported treatment-emergent adverse events (TEAEs). A summary of the number and percentage of subjects with TEAEs that occurred in at least 3% of the subjects during the study is provided in Table 11.

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Table 11. Number (%) of Subjects With Treatment-Emergent Adverse Events by Body System and Preferred Term (Incidence ≥3%), Safety Population

System Organ Class[a] Preferred Term	Placebo N=60	Giripladib 50 mg QD N=60	Giripladib 200 mg QD N=61	Giripladib 400 mg QD N=60	Giripladib 200 mg BID N=60	Naproxen 500 mg BID N=62	Total N=363
Any adverse event	37 (61.7)	41 (68.3)	44 (72.1)	42 (70.0)	46 (76.7)	47 (75.8)	257 (70.8)
Blood and lymphatic system disorders	0	0	0	2 (3.3)	0	0	2 (0.6)
Anaemia	0	0	0	2 (3.3)	0	0	2 (0.6)
Eye disorders	0	1 (1.7)	0	2 (3.3)	0	2 (3.2)	5 (1.4)
Gastrointestinal disorders	11 (18.3)	12 (20.0)	22 (36.1)	21 (35.0)	21 (35.0)	20 (32.3)	107 (29.5)
Abdominal distension	1 (1.7)	0	0	0	1 (1.7)	2 (3.2)	4 (1.1)
Abdominal pain	1 (1.7)	1 (1.7)	0	2 (3.3)	4 (6.7)	3 (4.8)	11 (3.0)
Abdominal pain upper	0	2 (3.3)	5 (8.2)	8 (13.3)	8 (13.3)	3 (4.8)	26 (7.2)
Aphthous stomatitis	0	0	0	0	0	2 (3.2)	2 (0.6)
Constipation	2 (3.3)	2 (3.3)	1 (1.6)	1 (1.7)	2 (3.3)	2 (3.2)	10 (2.8)
Diarrhoea	3 (5.0)	0	10 (16.4)	6 (10.0)	7 (11.7)	6 (9.7)	32 (8.8)
Dyspepsia	2 (3.3)	3 (5.0)	0	3 (5.0)	3 (5.0)	1 (1.6)	12 (3.3)
Flatulence	2 (3.3)	1 (1.7)	3 (4.9)	0	4 (6.7)	1 (1.6)	11 (3.0)
Frequent bowel movements	0	0	2 (3.3)	0	1 (1.7)	0	3 (0.8)
Gastrooesophageal reflux disease	1 (1.7)	1 (1.7)	1 (1.6)	2 (3.3)	1 (1.7)	2 (3.2)	8 (2.2)
Nausea	2 (3.3)	3 (5.0)	2 (3.3)	6 (10.0)	4 (6.7)	3 (4.8)	20 (5.5)
Stomach discomfort	2 (3.3)	1 (1.7)	0	0	0	0	3 (0.8)
Vomiting	2 (3.3)	0	0	1 (1.7)	0	0	3 (0.8)
General disorders and administration site conditions	2 (3.3)	7 (11.7)	4 (6.6)	4 (6.7)	4 (6.7)	4 (6.5)	25 (6.9)
Asthenia	0	2 (3.3)	0	0	1 (1.7)	0	3 (0.8)
Fatigue	1 (1.7)	0	2 (3.3)	2 (3.3)	2 (3.3)	0	7 (1.9)
Oedema peripheral	1 (1.7)	1 (1.7)	2 (3.3)	1 (1.7)	0	1 (1.6)	6 (1.7)

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Table 11. Number (%) of Subjects With Treatment-Emergent Adverse Events by Body System and Preferred Term (Incidence ≥3%), Safety Population

System Organ Class[a] Preferred Term	Placebo N=60	Giripladib 50 mg QD N=60	Giripladib 200 mg QD N=61	Giripladib 400 mg QD N=60	Giripladib 200 mg BID N=60	Naproxen 500 mg BID N=62	Total N=363
Pyrexia	0	2 (3.3)	0	1 (1.7)	0	0	3 (0.8)
Infections and infestations	9 (15.0)	11 (18.3)	10 (16.4)	10 (16.7)	11 (18.3)	10 (16.1)	61 (16.8)
Cystitis	1 (1.7)	2 (3.3)	2 (3.3)	0	1 (1.7)	0	6 (1.7)
Gastroenteritis	0	1 (1.7)	2 (3.3)	2 (3.3)	2 (3.3)	0	7 (1.9)
Nasopharyngitis	1 (1.7)	2 (3.3)	1 (1.6)	3 (5.0)	2 (3.3)	1 (1.6)	10 (2.8)
Oral herpes	0	0	1 (1.6)	0	2 (3.3)	0	3 (0.8)
Sinusitis	2 (3.3)	0	0	1 (1.7)	2 (3.3)	0	5 (1.4)
Urinary tract infection	2 (3.3)	2 (3.3)	2 (3.3)	2 (3.3)	1 (1.7)	2 (3.2)	11 (3.0)
Injury, poisoning and procedural complications	20 (33.3)	9 (15.0)	15 (24.6)	14 (23.3)	15 (25.0)	18 (29.0)	91 (25.1)
Accidental exposure	14 (23.3)	6 (10.0)	6 (9.8)	11 (18.3)	10 (16.7)	11 (17.7)	58 (16.0)
Accidental overdose	2 (3.3)	2 (3.3)	4 (6.6)	2 (3.3)	0	2 (3.2)	12 (3.3)
Contusion	0	0	1 (1.6)	0	0	2 (3.2)	3 (0.8)
Overdose	3 (5.0)	0	4 (6.6)	3 (5.0)	3 (5.0)	2 (3.2)	15 (4.1)
Investigations	1 (1.7)	6 (10.0)	6 (9.8)	6 (10.0)	5 (8.3)	2 (3.2)	26 (7.2)
Haematocrit decreased	0	2 (3.3)	0	1 (1.7)	0	0	3 (0.8)
Lipase increased	1 (1.7)	1 (1.7)	1 (1.6)	2 (3.3)	2 (3.3)	0	7 (1.9)
Metabolism and nutrition disorders	2 (3.3)	2 (3.3)	1 (1.6)	0	1 (1.7)	3 (4.8)	9 (2.5)
Hyperlipidaemia	1 (1.7)	1 (1.7)	0	0	1 (1.7)	2 (3.2)	5 (1.4)
Musculoskeletal and connective tissue disorders	6 (10.0)	11 (18.3)	10 (16.4)	9 (15.0)	15 (25.0)	9 (14.5)	60 (16.5)
Arthralgia	1 (1.7)	5 (8.3)	3 (4.9)	3 (5.0)	4 (6.7)	2 (3.2)	18 (5.0)
Back pain	0	0	2 (3.3)	2 (3.3)	2 (3.3)	3 (4.8)	9 (2.5)
Joint effusion	0	0	0	2 (3.3)	1 (1.7)	0	3 (0.8)

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Table 11. Number (%) of Subjects With Treatment-Emergent Adverse Events by Body System and Preferred Term (Incidence ≥3%), Safety Population

System Organ Class[a] Preferred Term	Placebo N=60	Giripladib 50 mg QD N=60	Giripladib 200 mg QD N=61	Giripladib 400 mg QD N=60	Giripladib 200 mg BID N=60	Naproxen 500 mg BID N=62	Total N=363
Joint swelling	2 (3.3)	0	0	0	0	0	2 (0.6)
Muscle spasms	1 (1.7)	0	1 (1.6)	0	3 (5.0)	2 (3.2)	7 (1.9)
Osteoarthritis	0	1 (1.7)	2 (3.3)	0	1 (1.7)	0	4 (1.1)
Pain in extremity	0	2 (3.3)	0	2 (3.3)	0	1 (1.6)	5 (1.4)
Nervous system disorders	6 (10.0)	7 (11.7)	6 (9.8)	11 (18.3)	4 (6.7)	5 (8.1)	39 (10.7)
Dizziness	2 (3.3)	0	0	1 (1.7)	0	0	3 (0.8)
Headache	5 (8.3)	3 (5.0)	4 (6.6)	8 (13.3)	3 (5.0)	3 (4.8)	26 (7.2)
Somnolence	0	2 (3.3)	0	0	1 (1.7)	0	3 (0.8)
Psychiatric disorders	0	0	1 (1.6)	3 (5.0)	2 (3.3)	2 (3.2)	8 (2.2)
Renal and urinary disorders	0	1 (1.7)	2 (3.3)	3 (5.0)	2 (3.3)	1 (1.6)	9 (2.5)
Dysuria	0	0	0	0	2 (3.3)	0	2 (0.6)
Respiratory, thoracic and mediastinal disorders	1 (1.7)	2 (3.3)	1 (1.6)	3 (5.0)	3 (5.0)	2 (3.2)	12 (3.3)
Pharyngolaryngeal pain	1 (1.7)	1 (1.7)	0	2 (3.3)	0	0	4 (1.1)
Skin and subcutaneous tissue disorders	2 (3.3)	3 (5.0)	2 (3.3)	1 (1.7)	2 (3.3)	1 (1.6)	11 (3.0)
Dermatitis contact	0	0	2 (3.3)	0	0	0	2 (0.6)
Vascular disorders	2 (3.3)	0	1 (1.6)	8 (13.3)	4 (6.7)	6 (9.7)	21 (5.8)
Hot flush	1 (1.7)	0	0	3 (5.0)	0	0	4 (1.1)
Hypertension	0	0	1 (1.6)	4 (6.7)	3 (5.0)	5 (8.1)	13 (3.6)

Classifications of adverse events are based on the Medical Dictionary for Regulatory Activities.
BID = twice daily, N = total number of subjects per treatment group, QD = once daily.
a. Totals at a higher level are not necessarily the sum of those at the lower levels since a subject might report ≥2 different adverse events within the higher level category.

A total of 85 subjects had SAEs. A summary of the number of subjects reporting SAEs during the study is provided in Table 12. The most frequently reported SAEs were: accidental exposure (58, 16%); overdose (15, 4.1%); accidental overdose (12, 3.3%); and drug administration error (3, 0.8%). Of all the reported SAEs, 2 SAEs ie chest pain occurred on Day 19 in the naproxen 500 mg BID treatment group and gastric ulcer occurred on Day 61 (poststudy) in giripladib 50 mg QD treatment group were found to be related to study drug by the Investigator.

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Table 12. Number (%) of Subjects Reporting Serious Adverse Events

System Organ Class[a] Preferred Term	Placebo N=60	Giripladib 50 mg QD N=60	Giripladib 200 mg QD N=61	Giripladib 400 mg QD N=60	Giripladib 200 mg BID N=60	Naproxen 500 mg BID N=62	Total N=363
Any adverse event	18 (30.0)	10 (16.7)	14 (23.0)	13 (21.7)	14 (23.3)	16 (25.8)	85 (23.4)
Gastrointestinal disorders	0	1 (1.7)	0	0	0	0	1 (0.3)
Gastric ulcer	0	1 (1.7)	0	0	0	0	1 (0.3)
General disorders and administration site conditions	0	0	0	0	0	1 (1.6)	1 (0.3)
Chest pain	0	0	0	0	0	1 (1.6)	1 (0.3)
Injury, poisoning and procedural complications	18 (30.0)	8 (13.3)	14 (23.0)	13 (21.7)	14 (23.3)	15 (24.2)	82 (22.6)
Accidental exposure	14 (23.3)	6 (10.0)	6 (9.8)	11 (18.3)	10 (16.7)	11 (17.7)	58 (16.0)
Accidental overdose	2 (3.3)	2 (3.3)	4 (6.6)	2 (3.3)	0	2 (3.2)	12 (3.3)
Drug administration error	0	0	1 (1.6)	0	1 (1.7)	1 (1.6)	3 (0.8)
Overdose	3 (5.0)	0	4 (6.6)	3 (5.0)	3 (5.0)	2 (3.2)	15 (4.1)
Skin and subcutaneous tissue disorders	0	1 (1.7)	0	0	0	0	1 (0.3)
Skin ulcer	0	1 (1.7)	0	0	0	0	1 (0.3)

Classifications of adverse events are based on the Medical Dictionary for Regulatory Activities.
BID = twice daily, N = total number of subjects per treatment group, QD = once daily.

a. Totals at a higher level are not necessarily the sum of those at the lower levels since a subject might report ≥2 different adverse events within the higher level category.

A total of 134 subjects discontinued from the study, of whom 37 discontinued because of AEs: 11 (18.3%) in the giripladib 200-mg BID group, 8 (12.9%) in the naproxen 500-mg BID group, 7 (11.5%) in the giripladib 200-mg QD group, 6 (10%) in the placebo group, 3 (5%) in the giripladib 400-mg QD group, and 2 (3.3%) in the giripladib 50-mg QD group as shown in Table 13.

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Table 13. Number and Percentage of Subjects Reporting Adverse Events Causing Withdrawal

System Organ Class[a] Preferred Term	Placebo N=60	Giripladib 50 mg QD N=60	Giripladib 200 mg QD N=61	Giripladib 400 mg QD N=60	Giripladib 200 mg BID N=60	Naproxen 500 mg BID N=62	Total N=363
Any adverse event	6 (10.0)	2 (3.3)	7 (11.5)	3 (5.0)	11 (18.3)	8 (12.9)	37 (10.2)
Blood and lymphatic system disorders	0	0	0	1 (1.7)	0	0	1 (0.3)
Anaemia	0	0	0	1 (1.7)	0	0	1 (0.3)
Gastrointestinal disorders	2 (3.3)	1 (1.7)	2 (3.3)	1 (1.7)	7 (11.7)	6 (9.7)	19 (5.2)
Abdominal distension	0	0	0	0	1 (1.7)	2 (3.2)	3 (0.8)
Abdominal pain	0	1 (1.7)	0	0	0	2 (3.2)	3 (0.8)
Abdominal pain upper	0	0	1 (1.6)	1 (1.7)	3 (5.0)	0	5 (1.4)
Constipation	0	1 (1.7)	0	0	1 (1.7)	0	2 (0.6)
Diarrhoea	0	0	1 (1.6)	0	1 (1.7)	3 (4.8)	5 (1.4)
Flatulence	0	0	0	0	2 (3.3)	0	2 (0.6)
Gastrooesophageal reflux disease	0	0	0	0	0	2 (3.2)	2 (0.6)
Haematochezia	0	0	0	0	1 (1.7)	0	1 (0.3)
Melaena	1 (1.7)	0	0	0	0	0	1 (0.3)
Nausea	1 (1.7)	1 (1.7)	1 (1.6)	1 (1.7)	2 (3.3)	1 (1.6)	7 (1.9)
General disorders and administration site conditions	0	1 (1.7)	0	0	0	1 (1.6)	2 (0.6)
Asthenia	0	1 (1.7)	0	0	0	0	1 (0.3)
Chest pain	0	0	0	0	0	1 (1.6)	1 (0.3)
Infections and infestations	0	1 (1.7)	1 (1.6)	0	0	0	2 (0.6)
Helicobacter gastritis	0	0	1 (1.6)	0	0	0	1 (0.3)
Urinary tract infection	0	1 (1.7)	0	0	0	0	1 (0.3)
Investigations	1 (1.7)	0	2 (3.3)	0	3 (5.0)	0	6 (1.7)
Blood amylase increased	0	0	1 (1.6)	0	0	0	1 (0.3)
Blood urea increased	0	0	0	0	1 (1.7)	0	1 (0.3)
Lipase increased	1 (1.7)	0	1 (1.6)	0	2 (3.3)	0	4 (1.1)
Urine leukocyte esterase	1 (1.7)	0	0	0	0	0	1 (0.3)
Metabolism and nutrition disorders	1 (1.7)	1 (1.7)	0	0	0	0	2 (0.6)

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Table 13. Number and Percentage of Subjects Reporting Adverse Events Causing Withdrawal

System Organ Class[a] Preferred Term	Placebo N=60	Giripladib 50 mg QD N=60	Giripladib 200 mg QD N=61	Giripladib 400 mg QD N=60	Giripladib 200 mg BID N=60	Naproxen 500 mg BID N=62	Total N=363
Anorexia	0	1 (1.7)	0	0	0	0	1 (0.3)
Hyperlipidaemia	1 (1.7)	0	0	0	0	0	1 (0.3)
Hypertriglyceridaemia	1 (1.7)	0	0	0	0	0	1 (0.3)
Musculoskeletal and connective tissue disorders	1 (1.7)	1 (1.7)	2 (3.3)	1 (1.7)	1 (1.7)	1 (1.6)	7 (1.9)
Arthralgia	0	1 (1.7)	0	0	0	0	1 (0.3)
Back pain	0	0	0	0	0	1 (1.6)	1 (0.3)
Bone pain	0	0	1 (1.6)	0	0	0	1 (0.3)
Myalgia	0	0	0	1 (1.7)	0	0	1 (0.3)
Osteoarthritis	0	0	1 (1.6)	0	1 (1.7)	0	2 (0.6)
Tendonitis	1 (1.7)	0	0	0	0	0	1 (0.3)
Nervous system disorders	1 (1.7)	1 (1.7)	0	1 (1.7)	0	2 (3.2)	5 (1.4)
Burning sensation	0	0	0	0	0	1 (1.6)	1 (0.3)
Dizziness	0	0	0	1 (1.7)	0	0	1 (0.3)
Headache	1 (1.7)	1 (1.7)	0	0	0	1 (1.6)	3 (0.8)
Psychiatric disorders	0	0	0	0	1 (1.7)	0	1 (0.3)
Nervousness	0	0	0	0	1 (1.7)	0	1 (0.3)
Renal and urinary disorders	0	0	1 (1.6)	0	0	0	1 (0.3)
Renal impairment	0	0	1 (1.6)	0	0	0	1 (0.3)
Respiratory, thoracic and mediastinal disorders	0	0	0	0	1 (1.7)	0	1 (0.3)
Nasal congestion	0	0	0	0	1 (1.7)	0	1 (0.3)
Skin and subcutaneous tissue disorders	0	1 (1.7)	0	0	1 (1.7)	0	2 (0.6)
Erythema	0	0	0	0	1 (1.7)	0	1 (0.3)
Skin ulcer	0	1 (1.7)	0	0	0	0	1 (0.3)

Classifications of adverse events are based on the Medical Dictionary for Regulatory Activities.
BID = twice daily, N = total number of subjects per treatment group, QD = once daily.

a. Totals at a higher level are not necessarily the sum of those at the lower levels since a subject might report ≥2 different adverse events within the higher level category.

No deaths occurred in the study.

Forty-nine (49) subjects had potentially clinically important (PCI) laboratory test results on therapy: 11 (19.6%) in the giripladib 200-mg BID group, 10 (16.9%) in the giripladib 400-mg QD group, 9 (15%) in the giripladib 200-mg QD group, 7 (12.3%) in the giripladib 50-mg QD group, 6 (10%) in the placebo group, and 6 (9.8%) in the naproxen 500-mg BID group. The most common PCI laboratory test results were high lipase levels (20, 5.7%), high triglyceride concentrations (9, 2.5%), increase in urea levels (6, 1.7%), low hemoglobin levels (5, 1.4%), and high potassium and amylase levels (4, 1.1% each).

CONCLUSION:

Development of the oral formulation of giripladib was terminated at the Sponsor's request after the second interim analysis of this study showed that giripladib did not meet pre-specified efficacy criteria for continuation of the development program in OA. In addition, there were more reports of upper abdominal pain and elevation of serum lipase levels in subjects treated with giripladib relative to subjects treated with placebo and naproxen.

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