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PROPRIETARY DRUG NAME® / GENERIC DRUG NAME: Celebrex® / Celecoxib

PROTOCOL NO: A3191084

PROTOCOL TITLE: Double-Blind, Triple Dummy, Parallel-Group, Randomized, Six-Month Study to Compare Celecoxib (200 mg BID) With Diclofenac SR (75 mg BID) Plus Omeprazole (20 mg QD) for Gastrointestinal Events in Subjects With Osteoarthritis and Rheumatoid Arthritis at High-Risk of Gastrointestinal Adverse Events

Study Centers: A total of 196 centers took part in the study and randomized subjects; 5 each in Belgium, Costa Rica, Ecuador, Lithuania, India, Taiwan, Korea and Peru; 7 in Brazil; 8 each in Canada, Colombia, Czech Republic, Spain and South Africa; 11 each in China, Germany, and Russia; 3 each in Croatia, Estonia, Latvia, Netherlands, Serbia, Singapore and Sweden; 1 each in France, Greece, and Panama; 6 in Guatemala; 2 in Hong Kong; 4 in Portugal; 17 in Ukraine and 23 in the United Kingdom (UK).

Study Initiation Date and Final Completion Date: 31 October 2005 to 11 May 2009

Phase of Development: Phase 4

Study Objectives:

Primary Objective: To determine whether celecoxib is superior to combined therapy with diclofenac slow release (SR) and omeprazole for the incidence of clinically significant upper and/or lower gastrointestinal (GI) events (CSULGIEs) in high GI risk subjects with osteoarthritis (OA) and/or rheumatoid arthritis (RA).

Secondary Objective: To determine safety and tolerability of celecoxib in subjects treated with celecoxib compared to treatment with diclofenac SR plus omeprazole in subjects with OA and/or RA.

METHODS:

Study Design: This was a 6-month, double-blind, triple-dummy, parallel group, randomized, multicenter, international study comparing treatment between celecoxib and diclofenac plus omeprazole in high risk subjects with OA and/or RA. The purpose of this study was to compare the incidence of CSULGIEs in subjects treated for 6 months with oral celecoxib (200 mg twice daily [BID]) or with oral diclofenac SR (75 mg BID) plus omeprazole (20 mg once daily [QD]).

Subjects were randomized with stratification by history of gastroduodenal (GD) ulceration (yes or no) to receive either celecoxib plus omeprazole placebo and diclofenac SR placebo or diclofenac SR plus omeprazole and celecoxib placebo orally and daily for the duration of the treatment period (minimum 158 days and maximum 202 days). Subjects had 6 scheduled study visits. If a GI event was suspected (hematemesis, melena or hemoglobin [Hb] reduced ≥2 g/dL and/or hematocrit [Hct] ≥10 percentage points from baseline or other significant signs or symptoms suggestive of a GI adverse event [AE] that the investigator felt may have represented a clinically relevant event) then the subject was to come in for an Event Visit. This could occur any time from randomization until 14 days after Visit 6. At the Event Visit, the subject was instructed to stop all study medication.

The maximum and expected duration of exposure to the study drug for an individual subject was 202 days (approximately 6.7 months). Including the screening period, the total maximum expected study duration for an individual subject was 7.2 months.

The timetable of study procedures and evaluations is presented in Table 1.

Table 1. Schedule of Events

Month		**Month 0**	**Event Visit**	**Month 1**	**Event Visit**	**Month 2**	**Event Visit**	**Month 4**	**Event Visit**	**Month 6**	**Event Visit**	**Interview**
Procedures	**Day -14**	**Day 1 ±2 Days**		**Day 30 ±4 Days**		**Day 60 ±4 Days**		**Day 120 ±1 Week**		**Day 180 ±1 Week**		
Written informed consent	X											
Inclusion/exclusion criteria	X	X										
Medical history	X											
Physical examination	X		(X)		(X)		(X)		(X)	X	(X)	
Alcohol intake information	X		(X)		(X)		(X)		(X)	X	(X)	
Vital signs	X	X	(X)	X	(X)	X	(X)	X	(X)	X	(X)	
Electrocardiogram (ECG)	X											
Urine pregnancy test[a]	X											
Helicobacter pylori test[b]	X		(X)		(X)		(X)		(X)		(X)	
Patient's global arthritis assessment	X	X	(X)	X	(X)	X	(X)	X	(X)	X	(X)	
Clinical laboratory tests	X	X	(X)	X	(X)	X	(X)	X	(X)	X	(X)	
Concomitant medications	X	X	(X)	X	(X)	X	(X)	X	(X)	X	(X)	
Pharmacogenomics blood samples		X										
Adverse events		X	(X)	X	(X)	X	(X)	X	(X)	X	(X)	
Randomization		X										
Dispense study medication		X		X		X		X				
Medication return/accountability			(X)	X	(X)	X	(X)	X	(X)	X	(X)	
Esophogastroduodenoscopy (EGD)	X[c]		(X)		(X)		(X)		(X)		(X)	
Colonoscopy			(X)		(X)		(X)		(X)		(X)	
Fecal occult bloods[d]	(X)[e]		(X)		(X)		(X)		(X)		(X)	
Additional laboratory tests[f]			(X)		(X)		(X)		(X)		(X)	
Subject summary										X		X[g]

Table 1. Schedule of Events

^{13}C = carbon-13; ^{14}C = carbon-14.

a. Required for all females of childbearing potential at screening. Could also be repeated during the study as per request of Independent Ethics Committees/Institutional Review Boards or if required by local regulations. The investigator had to ensure that subjects were not pregnant prior to first dose of study medication.
b. Serology, rapid urease/histology, ^{13}C or ^{14}C breathe test or fecal antigen as per local standard. Subjects with positive serology had active infection excluded using a second methodology. Repeated in case of Event Visit.
c. Only if required as a result of recent active ulceration with no follow-up.
d. Performed using any test as per local standard.
e. Performed only if required locally.
f. If subject was anemic: complete blood count with peripheral smear for manual review; lactate dehydrogenase, bilirubin, haptoglobin, reticulocyte count, folate, B12, ferritin, and total iron binding capacity.
g. Post-study subject interview. The investigator had to make reasonable efforts to obtain follow-up mortality and hospitalization information from each subject at 6 months (+ 2 weeks/ - 3 days) after study drug was stopped (due to early termination or regular study completion). This information was to be obtained by telephone and the subject had to be consented in advance.

Number of Subjects (Planned and Analyzed): Approximately 4402 subjects were planned to ensure 2201 subjects per arm. A total of 8098 subjects were screened, of which 4484 subjects (24 in Belgium, 586 in Brazil, 120 in Canada, 202 in China, 295 in Colombia, 277 in Costa Rica, 8 in Croatia, 113 in Czech Republic, 96 in Ecuador, 57 in Estonia, 7 in France, 187 in Germany, 3 in Greece, 42 in Guatemala, 87 in Hong Kong, 126 in India, 107 in Korea, 15 in Latvia, 320 in Lithuania, 18 in the Netherlands, 6 in Panama, 450 in Peru, 16 in Portugal, 134 in Russia, 339 in Serbia, 12 in Singapore, 130 in South Africa, 96 in Spain, 26 in Sweden, 54 in Taiwan, 261 in Ukraine and 270 in the UK) were assigned to study treatment and 4460 subjects were treated; 2223 subjects received celecoxib and 2237 subjects received diclofenac and omeprazole.

Diagnosis and Main Criteria for Inclusion: Subjects aged ≥60 years with or without a history of GD ulceration, or aged ≥18 years with documented evidence of GD ulceration 90 days or more prior to the screening visit, with a clinical diagnosis of OA or RA, and who were expected to require regular anti-inflammatory therapy for arthritis symptom management, were eligible for inclusion in the study.

Study Treatment: Subjects were randomized to 2 treatment groups (in a 1:1 ratio). Each group received either celecoxib (200 mg BID) plus omeprazole placebo and diclofenac SR placebo or diclofenac SR (75 mg BID) plus omeprazole (20 mg QD) and celecoxib placebo. All drugs were to be taken orally and daily for the duration of the treatment period (minimum 158 days and maximum 202 days).

Subjects were instructed to take study medication 2 times daily for 6 months. Subjects were instructed to start the study medication at the baseline visit. The study medication and dosing regimen are presented in Table 2.

Table 2. Study Medication and Dosing Regimen

Celecoxib Arm		
AM Dose	3 capsules	Celecoxib + diclofenac/placebo + omeprazole/placebo
PM Dose	2 capsules	Celecoxib + diclofenac/placebo
Diclofenac + Omeprazole Arm		
AM Dose	3 capsules	Celecoxib/placebo + diclofenac + omeprazole
PM Dose	2 capsules	Celecoxib/placebo + diclofenac

Efficacy and Safety Endpoints:

Primary Endpoint:

- Incidence of CSULGIEs. For the purposes of this study CSULGIEs were considered any event that in clinical practice would impact the subject in terms of inpatient or outpatient investigation for GI pathology with blood loss or other serious complication.

CSULGIEs were a composite of any of the following (adjudicated by GI Events Adjudication Committee):

- GD hemorrhage.

- Gastric outlet obstruction.
- GD, small bowel or large bowel perforation.
- Small bowel hemorrhage.
- Large bowel hemorrhage.
- Clinically significant anemia of defined GI origin.
- Acute GI hemorrhage of unknown origin, including presumed small bowel hemorrhage.
- Clinically significant anemia of presumed occult GI origin including possible small bowel blood loss.

Secondary Endpoints:

- The incidence of CSULGIEs plus symptomatic ulcers (SUs).
- The Patients Global Assessment of Arthritis.
- Change in Hb and Hct from baseline to Visit 6.
- The incidence of subjects who have a clinically significant decrease in Hct and/or Hb (clinically significant change is defined as fall in Hct >10% points and/or Hb ≥2 g/dL) from baseline.
- Hepatic AEs in gamma glutamyl-transferase (GGT), serum glutamic oxaloacetic transaminase (SGOT) (aspartate aminotransferase [AST]) or serum glutamic-pyruvic transaminase (SGPT) (alanine aminotransferase [ALT]) of 3 x upper limit of normal (ULN).
- Change in the hepatic measures of GGT, SGOT (AST) or SGPT (ALT) from baseline to Visit 6.
- Incidence of: (1) CSULGIEs, (2) SUs (3) moderate to severe abdominal symptoms and (4) withdrawal due to GI AEs.
- Change in the Iron parameters and C-Reactive Protein (CRP) from baseline to Visit 6.

Safety Evaluations: AEs were monitored and clinical laboratory evaluations and physical examinations were performed. Additional information on potential cardiovascular (CV) cases was obtained and submitted to a blinded CV Events Committee for adjudication of all events related to the CV system.

Statistical Methods:

- Safety Population: included subjects who were randomized and received at least 1 dose of study medication. The safety population was used for the safety analysis.

- Intent-to-treat (ITT) Population: included all randomized subjects.

The primary endpoint, incidence of CSULGIEs over 6 months, was analyzed by comparing the incidence of CSULGIEs between celecoxib and diclofenac SR plus omeprazole using a life-table (actuarial) extension of the Mantel-Haenszel method with a 2-sided test of the equality of proportions of subjects with CSULGIEs. The secondary endpoints of the incidence of combined CSULGIEs plus SUs, and the incidences of SUs, moderate to severe abdominal symptoms and withdrawal due to GI AEs were similarly analyzed. The change from baseline in the Patient's Global Assessment of arthritis score, using last observation carried forward, was analyzed using general linear models including history of GD ulceration and region as fixed effects, with the baseline score included as a covariate. These analyses were performed using the ITT population. Other secondary endpoints were analyzed using the safety population.

There were no formal statistical analyses of the safety data.

RESULTS

Subject Disposition and Demography: Subject disposition is summarized in Table 3. Of the total 4460 subjects who were treated, 3351 subjects (75.1%) completed the study and 1109 subjects (24.9%) discontinued; the percentage of subjects completing was greater for the celecoxib group (77.8% compared to 72.5% for the diclofenac and omeprazole group). For 2 subjects in the diclofenac and omeprazole group, the deaths occurred months after the study treatment was stopped; consequently, these 2 deaths were not captured in the clinical database and so are not summarized in Table 3.

Table 3. Subject Evaluation Groups

Number (%) of Subjects	Celecoxib 200 mg BID	Diclofenac SR 75 mg BID + Omeprazole 20 mg QD
Screened 8098		
Assigned to study treatment	2238	2246
Treated	2223	2237
Completed	1730 (77.8)	1621 (72.5)
Discontinued	493 (22.2)	616 (27.5)
Related to study drug	191 (8.6)	303 (13.5)
Adverse event	165 (7.4)	255 (11.4)
Laboratory abnormality	5 (0.2)	22 (1.0)
Lack of efficacy	21 (0.9)	26 (1.2)
Not related to study drug	300 (13.5)	311 (13.9)
Adverse event	68 (3.1)	50 (2.2)
Laboratory abnormality	4 (0.2)	11 (0.5)
Lost to follow-up	29 (1.3)	32 (1.4)
Other	87 (3.9)	76 (3.4)
No longer willing to participate	112 (5.0)	142 (6.4)
Subject died	2 (0.1)	2 (0.1)
ITT population	2238	2246
Analyzed for safety		
Adverse events	2223 (100.0)	2237 (100.0)
Laboratory data	2181 (98.1)	2168 (96.9)

BID = twice daily; ITT = intent-to-treat; QD = once daily; SR = slow release.

The majority of subjects (>80%) were female (Table 4). The mean age was approximately 65 years for both treatment groups. Most subjects (>85%) in both groups were aged ≥60 years.

Table 4. Summary of Demographic Characteristics – ITT Population

	Celecoxib 200 mg BID (N=2238)	Diclofenac SR 75 mg BID + Omeprazole 20 mg QD (N=2246)
Sex, number (%) of subjects		
Male	390 (17.4)	424 (18.9)
Female	1848 (82.6)	1822 (81.1)
Age, years		
Mean (SD)	65.2 (7.8)	65.3 (7.6)
Range	26-89	25-93
Race, number (%) of subjects		
White	1238 (55.3)	1212 (54.0)
Black	49 (2.2)	57 (2.5)
Asian	299 (13.4)	311 (13.8)
Hispanic	462 (20.6)	464 (20.7)
Other	190 (8.5)	202 (9.0)

BID = twice daily; ITT = intent-to-treat; N = number of subjects; QD = once daily; SD = standard deviation; SR = slow release.

Efficacy Results:

Primary Endpoint Results**:**

Incidence of CSULGIEs: Overall, there were 20/2238 subjects (0.9%) in the celecoxib group and 81/2246 subjects (3.6%) in the diclofenac and omeprazole group who were adjudicated as having CSULGIEs (odds ratio 4.32) (Table 5). The incidence of CSULGIEs was significantly lower for the celecoxib group compared to the diclofenac and omeprazole group (p-value = <0.0001).

Table 5. Summary of Incidence of Adjudicated CSULGIEs – ITT Population

	Celecoxib 200 mg BID		Diclofenac SR 75 mg BID +Omeprazole 20 mg QD	
	Subjects at Risk	**Number (%) of Subjects with CSULGIE**	**Subjects at Risk**	**Number (%) of Subjects with CSULGIE**
All subjects	2238	20 (0.9)	2246	81 (3.6)
Odds ratio				4.32
CMH statistic				41.070
p-value[a]				<0.0001

BID = twice daily; CSULGIEs = clinically significant upper and/or lower gastrointestinal events; CMH = Cochran-Mantel-Haenszel; GD = gastroduodenal; ITT = intent-to-treat; OA = osteoarthritis; QD = once daily; RA = rheumatoid arthritis; SR = slow release.

a. Actuarial (life table) extension of CMH statistics with time-block (Visit 3 to Visit 6), stratified by region and history of GD ulceration

The most common component of the CSULGIE composite endpoint was clinically significant anemia of occult GI origin; such events comprised more than half of all CSULGIEs: 10/20 CSULGIEs in the celecoxib group and 53/81 CSULGIEs in the diclofenac and omeprazole group (Table 6).

Table 6. Summary of CSULGIEs by Specific Event

Number (%) of Subjects With Event	Celecoxib 200 mg BID (N=2238)	Diclofenac SR 75 mg BID + Omeprazole 20 mg QD (N=2246)
Gastrododenal hemorrhage	3 (0.1)	3 (0.1)
Large bowel hemorrhage	1 (<0.1)	1 (<0.1)
Clinically significant anemia of defined GI origin	5 (0.2)	24 (1.1)
Acute GI hemorrhage of unknown origin	1 (<0.1)	0
Clinically significant anemia of presumed occult GI origin	10 (0.4)	53 (2.4)
Total: Clinically significant GI events	20 (0.9)	81 (3.6)

BID = twice daily; CSULGIEs = clinically significant upper and/or lower gastrointestinal events; GI = gastrointestinal; ITT = intent-to-treat; QD = once daily; SR = slow release.

Secondary Endpoint Results:

Incidence of CSULGIEs Plus SUs: Table 7 summarizes the overall incidence of CSULGIEs or SUs (where a subject had no CSULGIE indication) within each treatment group by history

of GD ulceration. Overall, there were 25/2238 subjects (1.1%) in the celecoxib group and 92/2246 subjects (4.1%) in the diclofenac and omeprazole group who were adjudicated as having CSULGIEs or SUs, with an odds ratio of 3.93. This difference was statistically significant (p <0.0001).

Table 7. Summary of Incidence of Adjudicated CSULGIEs or Symptomatic Ulcers – ITT Population

Number (%) of Subjects With CSULGIEs or Symptomatic Ulcers	Celecoxib 200 mg BID (N=2238)	Diclofenac SR 75 mg BID + Omeprazole 20 mg QD (N=2246)
Overall	25 (1.1)	92 (4.1)
Without a history of GD ulceration	16 (0.7)	73 (3.3)
With a history of GD ulceration	9 (0.4)	19 (0.8)
Odds ratio		3.93
CMH statistic		43.040
p-value		<0.0001

Odds ratio, CMH statistic and p-value calculated using actuarial (life table) extension of CMH statistics, stratified by region, history of GD ulceration and time-blocks.
BID = twice daily; CSULGIE = clinically significant upper and/or lower gastrointestinal events; CMH = Cochran-Mantel-Haenszel; GD = gastroduodenal; ITT = intent-to-treat; QD = once daily; SR = slow release.

Patient's Global Assessment of Arthritis: Overall, there was no significant treatment difference in terms of the changes from baseline in the Patient's Global Arthritis Assessment at the final visit or early termination (Table 8). For both treatments, the proportion of subjects giving an assessment of 'good' or 'very good' increased from approximately 10% at baseline to approximately 40% to 60% at all postbaseline time points (Months 1, 2, 4 and 6).

Table 8. Summary of Changes From Baseline in Patient's Global Arthritis Assessment at Final Visit or Early Termination (LOCF) – ITT Population

	Celecoxib 200 mg BID (N=2238)	Diclofenac SR 75 mg BID + Omeprazole 20 mg QD (N=2246)
Number (%) of subjects in the analysis	2207 (98.6)	2213 (98.5)
Mean (SD) change from baseline	0.8 (0.9)	0.8 (0.9)
LS Mean (SE) change from baseline	0.754 (0.020)	0.773 (0.019)
Difference (SE)in LS means		-0.019 (0.023)
95% CI		-0.06, 0.03
p-value[a]		0.4146
p-value[b]		0.6529

BID = twice daily; CI = confidence interval; GD = gastroduodenal; ITT = intent-to-treat; LOCF = last observation carried forward; LS = least squares; QD = once daily; SR = slow release; SD = standard deviation; SE = standard error.
a. General linear model, least squares mean and p-value from general linear model with fixed effects of site and history of GD ulceration with a covariate of patient's global arthritis assessment at baseline.
b. VanElterns test stratified by site.

Changes in Hb and Hct From Baseline: Overall, there was a more marked mean decrease in Hb for the diclofenac and omeprazole group compared to the celecoxib group (Table 9).

This difference was statistically significant (p <0.0001). A similar trend was seen with Hct (Table 10). On the Event Visit, subjects with potential events showed a decrease in Hb.

Table 9. Summary of Changes From Baseline in Hemoglobin (g/dL) – Safety Population

	Celecoxib 200 mg BID (N=2223)	Diclofenac SR 75 mg BID + Omeprazole 20 mg QD (N=2237)
Baseline		
Mean (SD)	13.6 (1.1)	13.6 (1.1)
n	2184	2167
Month 6/early termination		
Mean (SD) change from baseline	-0.0 (0.7)	-0.4 (0.8)
n	2018	1939
Event		
Mean (SD) change from baseline	-0.5 (2.3)	-1.3 (1.2)
n	58	156
Overall		
Mean (SD) change from baseline	-0.0 (0.7)	-0.4 (0.8)
n	2184	2167
LS Mean (SE) change from baseline	-0.017 (0.019)	-0.423 (0.019)
Difference (SE)in LS means		0.406 (0.022)
95% CI		0.36, 0.45
p-value[a]		<0.0001

BID = twice daily; CI = confidence interval; LS = least squares; QD = once daily; SE = standard error; SD = standard deviation; SR = slow release.

a. General linear model, least squares mean and p-value from general linear model with fixed effects of region and history of gastroduodenal ulceration with a covariate of hemoglobin at baseline.

Table 10. Summary of Changes From Baseline in Hematocrit (%) – Safety Population

	Celecoxib 200 mg BID (N=2223)	Diclofenac SR 75 mg BID + Omeprazole 20 mg QD (N=2237)
Baseline		
Mean (SD)	41.4 (3.5)	41.4 (3.5)
n	2184	2167
Month 6/early termination		
Mean (SD) change from baseline	-0.3 (2.3)	-1.4 (2.4)
n	2018	1938
Event		
Mean (SD) change from baseline	-2.5 (3.7)	-3.5 (3.5)
n	58	156
Overall		
Mean (SD) change from baseline	-0.3 (2.3)	-1.4 (2.5)
n	2184	2167
LS Mean (SE) change from baseline	-0.306 (0.059)	-1.425 (0.059)
Difference (SE)in LS Means		1.118 (0.069)
95% CI		0.98, 1.25
p-value[a]		<0.0001

BID = twice daily; CI = confidence interval; LS = least squares; QD = once daily; SD = standard deviation; SE = standard error; SR = slow release.

a. General linear model, least squares mean and p-value from general linear model with fixed effects of region and history of gastroduodenal ulceration with a covariate of hematocrit at baseline.

Incidence of Subjects With a Clinically Significant Decrease in Hb and/or Hct From Baseline: The proportion of subjects with a clinically significant decrease in Hb (decrease ≥2 g/dL) and/or Hct (decrease ≥10%) was significantly greater for the diclofenac and omeprazole group compared to the celecoxib group (Table 11). The proportion of subjects with a clinically significant decrease in Hct (decrease ≥10%) was not significantly different between the groups.

Table 11. Summary of Incidence of Clinically Significant Decrease in Subject's Hemoglobin or Hematocrit Values – Safety Population

	Celecoxib 200 mg BID (N=2223)	Diclofenac SR 75 mg BID + Omeprazole 20 mg QD (N=2237)
Number of subjects in the analysis	2184	2176
Number (%) of subjects with:		
Decrease in hemoglobin ≥2 g/dL	44 (2.0)	123 (5.7)
Decrease in hemoglobin <2 g/dL, or increase	2140 (98.0)	2044 (94.3)
Relative Risk		2.812
95% CI of relative risk		2.00, 3.94
p-value[a]		<0.0001
Decrease in hematocrit ≥10%	8 (0.4)	16 (0.7)
Decrease in hematocrit <10%, or increase	2176 (99.6)	2151 (99.3)
Relative risk		1.992
95% CI of Relative Risk		0.86, 4.63
p-value[a]		0.1024
Number (%) of Subjects with:		
Month 6/Early Termination		
n	2018	1939
Decrease in hemoglobin ≥2 g/dL and/or decrease in hematocrit ≥10%	14 (0.7)	54 (2.8)
Decrease in hemoglobin <2 g/dL, or increase and/or decrease in hematocrit <10%, or increase	2004 (99.3)	1885 (97.2)
Event		
n	58	156
Decrease in hemoglobin ≥2 g/dL and/or decrease in hematocrit ≥10%	8 (13.8)	38 (24.4)
Decrease in hemoglobin <2 g/dL, or increase and/or decrease in hematocrit <10%, or increase	50 (86.2)	118 (75.6)
Overall		
n	2184	2167
Decrease in hemoglobin ≥2 g/dL and/or decrease in hematocrit ≥10%	45 (2.1)	123 (5.7)
Decrease in hemoglobin <2 g/dL, or increase and/or decrease in hematocrit <10%, or increase	2139 (97.9)	2044 (94.3)
Relative risk		2.748
95% CI of relative risk		1.96, 3.84
p-value[a]		<0.0001

Clinically significant decreases were ≥2 g/dL for hemoglobin and ≥10% for hematocrit.
BID = twice daily; CI = confidence interval; N = number of subjects; n = number of subject in analysis at time point; QD = once daily; SR = slow release.
a. Cochran-Mantel-Haenszel method, with stratification by region and history of gastroduodenal ulceration.

Hepatic AEs: At baseline, most subjects (>95%) had GGT, ALT and/or AST values <3 x ULN (Table 12). Postbaseline, the number of subjects with GGT or ALT ≥3 x ULN was markedly greater for the diclofenac and omeprazole compared to the celecoxib group; these treatment differences were statistically significant. The number of subjects with postbaseline AST ≥3 x ULN was similar for both treatment groups and the treatment difference was not statistically significant.

Table 12. Incidence of Clinically Significant Hepatic Adverse Events – Safety Population

Number (%) of Subjects	Celecoxib 200 mg BID (N=2223)		Diclofenac SR 75 mg BID + Omeprazole 20 mg QD (N=2237)	
	Baseline		Baseline	
GGT	≥3 x ULN	<3 x ULN	≥3 x ULN	<3 x ULN
	12 (0.5)	2174 (97.8)	18 (0.8)	2154 (96.3)
Postbaseline GGT ≥3 x ULN	6 (50.0)	20 (0.9)	16 (88.9)	70 (3.2)
Postbaseline GGT <3 x ULN	6 (50.0)	2154 (99.1)	2 (11.1)	2084 (96.8)
Treatment comparison (baseline)			Relative risk	1.510
			95% CI	0.729, 3.126
			p-value[a]	0.2779
Treatment comparison (Postbaseline)			Relative risk	3.329
			95% CI	2.156, 5.141
			p-value[a]	4.214×10^{-9}
	Baseline		Baseline	
ALT	≥3 x ULN	<3 x ULN	≥3 x ULN	<3 x ULN
Baseline	3 (0.1)	2174 (97.8)	0	2164 (96.7)
Postbaseline ALT ≥3 x ULN	0	13 (0.6)	0	27 (1.2)
Postbaseline ALT <3 x ULN	3 (100.0)	2161 (99.4)	0	2137 (98.8)
Treatment comparison (baseline)			Relative risk	NR
			95% CI	NR
			p-value[a]	0.2498
Treatment comparison (Postbaseline)			Relative risk	2.089
			95% CI	1.081, 4.038
			p-value[a]	0.0264
AST	≥3 x ULN	<3 x ULN	≥3 x ULN	<3 x ULN
Baseline	2 (0.1)	2175 (97.8)	0	2164 (96.7)
Post-Baseline AST ≥3 x ULN	0	8 (0.4)	0	12 (0.6)
Post-Baseline AST <3 x ULN	2 (100.0)	2167 (99.6)	0	2152 (99.4)
Treatment comparison (baseline)			Relative risk	NR
			95% CI	NR
			p-value[a]	0.4999
Treatment comparison (Postbaseline)			Relative risk	1.509
			95% CI	0.618, 3.684
			p-value[a]	0.3809

ALT = alanine aminotransferase; AST = aspartate aminotransferase; BID = twice daily; CI = confidence interval; GGT = gamma glutamyl-transferase; NR = not recorded; QD = once daily; SR = slow release; ULN = upper limit of normal.
a. Fisher's Exact Test.

Changes From Baseline in Hepatic Measures: Overall, there was a mean decrease compared to baseline in the hepatic measures (GGT, ALT and AST) for the celecoxib group compared to a mean increase for the diclofenac and omeprazole group (Table 13); this treatment difference was statistically significant.

Table 13. Summary of Changes From Baseline in Hepatic Measures – Safety Population

		Celecoxib 200 mg BID (N=2223)	Diclofenac SR 75 mg BID +Omeprazole 20 mg QD (N=2237)
GGT (IU/L)	Baseline - mean (SD)	27.2 (26.9)	26.4 (24.8)
	n	2186	2172
	Month 6/early termination		
	Mean (SD) change from baseline	-2.6 (19.1)	8.0 (28.3)
	n	2034	1961
	Overall		
	Mean (SD) change from baseline	-2.6 (19.6)	7.7 (27.1)
	n	2186	2172
	LS mean (SE) change from baseline	-2.689 (0.591)	7.455 (0.592)
	Difference (SE) in LS means		-10.144 (0.697)
	95% CI (p-value)[a]		-11.51, -8.78 (<0.0001)
ALT (IU/L)	Baseline - mean (SD)	21.8 (26.8)	21.2 (10.2)
	n	2177	2164
	Month 6/early termination		
	Mean (SD) change from baseline	-1.3 (28.6)	5.9 (17.8)
	n	1998	1926
	Overall		
	Mean (SD) change from baseline	-1.4 (27.1)	5.4 (15.6)
	n	2177	2164
	LS Mean (SE) change from baseline	-1.151 (0.364)	5.213 (0.364)
	Difference (SE) in LS means		-6.364 (0.428)
	95% CI (p-value)[a]		-7.20, -5.52 (<0.0001)
AST (IU/L)	Baseline - mean (SD)	23.6 (57.3)	22.5 (7.1)
	n	2177	2164
	Month 6		
	Mean (SD) change from baseline	-1.5 (59.5)	2.1 (10.3)
	n	1998	1927
	Overall		
	Mean (SD) change from baseline	-1.5 (57.1)	2.0 (9.8)
	n	2177	2164
	LS mean (SE) change from baseline	-0.901 (0.239)	1.490 (0.239)
	Difference (SE) in LS means		-2.391 (0.281)
	95% CI (p-value)[a]		-2.94, -1.84 (<0.0001)

ALT = alanine aminotransferase; AST = aspartate aminotransferase; BID = twice daily; CI = confidence interval; GGT = gamma glutamyl-transferase; GD = gastroduodenal; LS = least squares; QD = once daily; SD = standard deviation; SE = standard error; SR = slow release.

a. General linear model, least squares mean and p-value from linear model with fixed effects of region and history of GD ulceration with a covariate of baseline value.

Change from Baseline in Iron Parameters and CRP: Overall, there was a mean increase compared to baseline in iron binding capacity and a mean decrease in ferritin for both treatments (Table 14); for both parameters, there was no statistically significant treatment difference. Levels of CRP remained close to baseline throughout the study and there was no significant treatment difference.

Table 14. Summary of Changes from Baseline in Iron Parameters and C-Reactive Protein – Safety Population

		Celecoxib 200 mg BID (N=2223)	Diclofenac SR 75 mg BID + Omeprazole 20 mg QD (N=2237)
Iron binding capacity (µg/dL)	Baseline - Mean (SD)	361.0 (53.0)	362.2 (89.4)
	n	2185	2171
	Month 6		
	Mean (SD) change from baseline	1.4 (37.3)	0.1 (84.7)
	n	2034	1959
	Overall		
	Mean (SD) change from baseline	1.6 (37.7)	0.3 (81.8)
	n	2185	2171
	LS mean (SE) change from baseline	2.517 (1.158)	1.952 (1.161)
	Difference (SE) in LS means		0.565 (1.366)
	95% CI (p-value)[a]		-2.11, 3.24 (0.6795)
Ferritin (µg/L)	Baseline - Mean (SD)	132.0 (191.1)	127.0 (112.6)
	n	2185	2170
	Month 6		
	Mean (SD) change from baseline	-9.0 (148.5)	-5.4 (62.3)
	n	2030	1957
	Overall		
	Mean (SD) change from baseline	-8.6 (144.6)	-5.1 (63.4)
	n	2185	2170
	LS mean (SE) change from baseline	-3.396 (2.224)	-1.990 (2.228)
	Difference (SE) in LS means		-1.406 (2.624)
	95% CI (p-value)[a]		-6.55, 3.74 (0.5920)
C-reactive protein (mg/dL)	Baseline - Mean (SD)	0.6 (1.1)	0.6 (0.9)
	n	2185	2171
	Month 6		
	Mean (SD) change from baseline	0.0 (1.5)	0.1 (1.2)
	n	2030	1957
	Overall		
	Mean (SD) change from baseline	0.0 (1.6)	0.1 (1.2)
	n	2185	2171
	LS mean (SE) change from baseline	0.058 (0.032)	0.073 (0.032)
	Difference (SE) in LS means		-0.015 (0.038)
	95% CI (p-value)[a]		-0.09, 0.06 (0.6819)

BID = twice daily; CI = confidence interval; GD = gastroduodenal; LS = least squares; QD = once daily; SD = standard deviation; SE = standard error; SR = slow release.

a. General linear model, least squares mean and p-value from linear model with fixed effects of region and history of GD ulceration with a covariate of baseline value.

Withdrawal From Study due to GI AEs: The proportion of subjects withdrawn due to GI AEs was greater for the diclofenac and omeprazole group (7.4%) compared to the celecoxib group (5.1%); this difference was statistically significant (Table 15). The most common time-block for withdrawals was Day 1-45, which included 52/114 withdrawals (45.6%) for the celecoxib group and 91/167 withdrawals (54.5%) for the diclofenac and omeprazole group.

Table 15. Summary of Incidence of Withdrawal From Study due to Gastrointestinal Adverse Events – ITT Population

Number (%) of Subjects Who Withdrew From the Study due to Gastrointestinal Adverse Events	Celecoxib 200 mg BID (N=2238)	Diclofenac SR 75 mg BID + Omeprazole 20 mg QD (N=2246)
Overall	114 (5.1)	167 (7.4)
Without a history of GD ulceration	88 (3.9)	128 (5.7)
With a history of GD ulceration	26 (1.2)	39 (1.7)
Odds ratio		1.52
CMH statistic		11.640
p-value		0.0006

Gastrointestinal adverse events included terms that coded to the MedDRA System Organ Class term of 'gastrointestinal disorders', excluding terms that coded to the Higher Level Group Terms of 'benign neoplasms gastrointestinal', 'dental and gingival conditions', 'oral soft tissue conditions', 'salivary gland conditions', or 'tongue conditions'.
Odds ratio, CMH statistic and p-value calculated using actuarial (life table) extension of CMH statistics, stratified by region, history of GD ulceration and time-blocks.
BID = twice daily; CMH = Cochran-Mantel-Haenszel; GD = gastroduodenal; ITT = intent-to-treat; QD = once daily; SR = slow release.

Incidence of Moderate to Severe Abdominal Symptoms: The proportion of subjects with moderate to severe abdominal symptoms was greater for the diclofenac and omeprazole group (7.2%) compared to the celecoxib group (5.9%); this difference was statistically significant (Table 16). The difference appeared to be mainly in the subjects without a history of GD ulceration. The majority of the events occurred during the time-block Day 1-45.

Table 16. Summary of Incidence of Moderate to Severe Abdominal Symptoms – ITT Population

Number (%) of Subjects with Moderate to Severe Abdominal Symptoms	Celecoxib 200 mg BID (N=2238)	Diclofenac SR 75 mg BID + Omeprazole 20 mg QD (N=2246)
Overall	132 (5.9)	162 (7.2)
Without a history of GD ulceration	109 (4.9)	139 (6.2)
With a history of GD ulceration	23 (1.0)	23 (1.0)
Odds ratio		1.26
CMH statistic		3.860
p-value		0.0495

Abdominal symptoms included terms that coded to the MedDRA Higher Level Group Term of 'Gastrointestinal signs and symptoms'.
Odds ratio, CMH statistic and p-value calculated using actuarial (life table) extension of CMH statistics, stratified by region, history of GD ulceration and time-blocks.
BID = twice daily; CMH = Cochran-Mantel-Haenszel; GD = gastroduodenal; ITT = intent-to-treat; QD = once daily; SR = slow release.

Safety Results: An overall summary of treatment-emergent AEs is presented in (Table 17). Treatment-related AEs were reported for 25.3% and 32.9% of subjects in the celecoxib group and the diclofenac and omeprazole group, respectively. The proportion of subjects reporting serious adverse events (SAEs) was <3% for both groups (with <1% in each group reporting treatment-related SAEs). Most AEs were mild or moderate in severity; ≤5% of subjects in each group experienced a severe AE.

Table 17. Overall Summary of Adverse Events – Safety Population

	Celecoxib 200 mg BID		Diclofenac SR 75 mg BID + Omeprazole 20 mg QD	
Number (%) of Subjects	**All Causalities**	**Treatment Related**	**All Causalities**	**Treatment Related**
Evaluable for AEs	2223	2223	2237	2237
Number of AEs	2273	813	2789	1173
With AEs	1137 (51.1)	562 (25.3)	1287 (57.5)	736 (32.9)
With SAEs	61 (2.7)	13 (0.6)	61 (2.7)	8 (0.4)
With severe AEs	109 (4.9)	38 (1.7)	111 (5.0)	44 (2.0)
Discontinued due to AEs[a]	241 (10.8)	170 (7.6)	338 (15.1)	277 (12.4)
Dose reduced or temporary discontinuations due to AEs	130 (5.8)	48 (2.2)	210 (9.4)	103 (4.6)

AE = adverse event; BID = twice daily; QD = once daily; SAE = serious adverse event; SR = slow release.

a. Discrepancies between these totals and those presented in Table 3 reflect that this table summarizes data from the AE pages of the case report forms (CRFs), while Table 3 summarizes data from the discontinuation pages of the CRFs.

With regard to AE preferred terms, dyspepsia and diarrhea were the most frequently reported non-serious AEs across the 2 groups (Table 18). Dyspepsia was the most frequently reported AE for the celecoxib group (6.2% of subjects [5.8% treatment-related] compared to 5.0% of subjects [4.6% treatment-related] for the diclofenac and omeprazole group). Diarrhea was more frequently reported in subjects in the diclofenac and omeprazole group (7.5% of subjects [treatment-related for 3.1%]) than the celecoxib group (3.6% of subjects [treatment-related for 1.6%]). Abdominal pain upper was also frequently reported in both groups (4.3% [3.4% treatment-related] in the celecoxib group compared to 5.9% [5.3% treatment-related] for the diclofenac and omeprazole group) (Table 18 and Table 19).

Table 18. Treatment-Emergent Non-Serious Adverse Events by Special Organ Class and Preferred Term (All Causalities) for Events Having a Frequency Rate ≥2%

	Celecoxib 200 mg BID n (%)	Diclofenac SR 75 mg BID + Omeprazole 20 mg QD n (%)
Number (%) of Subjects:		
Evaluable for adverse events	2223	2237
With adverse events	530 (23.8)	669 (29.9)
Number (%) of Subjects with Adverse Events by:		
System Organ Class		
MedDRA (v12.0) preferred term		
Gastrointestinal disorders	335 (15.1)	457 (20.4)
Abdominal pain upper	96 (4.3)	133 (5.9)
Diarrhoea	79 (3.6)	168 (7.5)
Dyspepsia	137 (6.2)	111 (5.0)
Gastritis	32 (1.4)	44 (2.0)
Nausea	33 (1.5)	66 (3.0)
General disorders and administration site conditions	46 (2.1)	67 (3.0)
Oedema peripheral	46 (2.1)	67 (3.0)
Infections and infestations	55 (2.5)	46 (2.1)
Nasopharyngitis	55 (2.5)	46 (2.1)
Investigations	27 (1.2)	72 (3.2)
Haemoglobin decreased	27 (1.2)	72 (3.2)
Nervous system disorders	66 (3.0)	48 (2.1)
Headache	66 (3.0)	48 (2.1)
Vascular disorders	76 (3.4)	84 (3.8)
Hypertension	76 (3.4)	84 (3.8)

Subjects were only counted once per treatment for each row.
Included data up to 30 days after last dose of study drug.
MedDRA (v12.0) coding dictionary applied.
BID = twice daily; MedDRA = Medical Dictionary for Regulatory Activities; QD = once daily; SR = slow release.

Table 19. Summary of Most Frequent Adverse Events by Preferred Term – Safety Population (Treatment-Related)

Number (%) of Subjects	Celecoxib 200 mg BID	Diclofenac SR 75 mg BID + Omeprazole 20 mg QD
Dyspepsia	130 (5.8)	103 (4.6)
Abdominal pain upper	75 (3.4)	119 (5.3)
Diarrhea	35 (1.6)	70 (3.1)
Hypertension	47 (2.1)	52 (2.3)
Headache	24 (1.1)	17 (0.8)
Nasopharyngitis	2 (0.1)	3 (0.1)
Edema peripheral	29 (1.3)	45 (2.0)
Nausea	25 (1.1)	50 (2.2)
Gastritis	24 (1.1)	37 (1.7)
Hemoglobin decreased	12 (0.5)	47 (2.1)
Constipation	8 (0.4)	20 (0.9)

The AEs/SAEs results are not separated out.
AEs = adverse events; BID = twice daily; QD = once daily; SR = slow release; SAEs = serious adverse events.

SAEs were reported for 61/2223 subjects (2.7%) in the celecoxib group and by 61/2237 subjects (2.7%) in the diclofenac and omeprazole group (Table 20).

Table 20. Treatment-Emergent Serious Adverse Events by Special Organ Class and Preferred Term (All Causalities)

	Celecoxib 200 mg BID	Diclofenac SR 75 mg BID + Omeprazole 20 mg QD
	n (%)	n (%)
Number (%) of subjects:		
Evaluable for adverse events	2223	2237
With adverse events	61 (2.7)	61 (2.7)
Number (%) of subjects with adverse events by:		
System Organ Class		
MedDRA (v12.0) preferred term		
Blood and lymphatic system disorders	0	1
Normochromic normocytic anaemia	0	1
Cardiac disorders	4 (0.2)	2 (0.1)
Acute myocardial infarction	2 (0.1)	2 (0.1)
Angina unstable	1	0
Cardiogenic shock	1	0
Coronary artery stenosis	1	1
Myocardial infarction	1	0
Myocardial ischaemia	0	1
Ear and labyrinth disorders	1	0
Hypoacusis	1	0
Eye disorders	0	1
Glaucoma	0	1
Gastrointestinal disorders	8 (0.4)	10 (0.4)
Abdominal pain	1	1
Abdominal pain lower	0	1
Abdominal pain upper	0	1
Colitis	1	1
Constipation	0	2 (0.1)
Diarrhoea	0	2 (0.1)
Duodenal ulcer	2 (0.1)	0
Dyspepsia	0	1
Enteritis	1	0
Erosive oesophagitis	1	0
Gastric ulcer	2 (0.1)	2 (0.1)
Gastric ulcer haemorrhage	0	1
Gastritis	0	1
Gastritis erosive	0	1
Gastrointestinal haemorrhage	1	0
Inguinal hernia	0	1
Nausea	1	3 (0.1)
Reflux oesophagitis	1	0
Umbilical hernia	0	1
Vomiting	0	2 (0.1)
General disorders and administration site conditions	5 (0.2)	2 (0.1)
Chest pain	1	0
Death	0	1
Disease progression	1	0
Pyrexia	3 (0.1)	1
Hepatobiliary disorders	3 (0.1)	2 (0.1)

Table 20. Treatment-Emergent Serious Adverse Events by Special Organ Class and Preferred Term (All Causalities)

	Celecoxib 200 mg BID	Diclofenac SR 75 mg BID + Omeprazole 20 mg QD
	n (%)	n (%)
Cholangitis	0	1
Cholecystitis acute	1	0
Cholelithiasis	2 (0.1)	2 (0.1)
Infections and infestations	10 (0.4)	11 (0.5)
Acute sinusitis	1	0
Appendicitis	1	0
Arthritis bacterial	0	2 (0.1)
Bronchopneumonia	0	2 (0.1)
Burn infection	1	0
Cellulitis	2 (0.1)	1
Chronic sinusitis	0	1
Device related infection	1	0
Enterocolitis infectious	0	1
Erysipelas	1	0
Groin abscess	0	1
Osteomyelitis	0	1
Pulmonary tuberculosis	1	0
Pyothorax	1	0
Urinary tract infection	1	2 (0.1)
Injury, poisoning and procedural complications	8 (0.4)	9 (0.4)
Ankle fracture	0	2 (0.1)
Comminuted fracture	0	1
Concussion	1	0
Eye burns	1	0
Fall	1	0
Femur fracture	1	0
Forearm fracture	0	2 (0.1)
Gunshot wound	0	1
Injury	1	1
Joint sprain	0	1
Lumbar vertebral fracture	1	0
Medical device complication	0	1
Meniscus lesion	1	1
Muscle strain	1	0
Radius fracture	0	1
Rib fracture	1	0
Road traffic accident	1	2 (0.1)
Spinal compression fracture	1	0
Thoracic vertebral fracture	0	1
Tibia fracture	0	1
Traumatic brain injury	0	1
Upper limb fracture	1	0
Metabolism and nutrition disorders	1	2 (0.1)
Diabetes mellitus inadequate control	0	1
Hyperuricaemia	0	1
Hypoglycaemia	0	1
Hypokalaemia	1	1

Table 20. Treatment-Emergent Serious Adverse Events by Special Organ Class and Preferred Term (All Causalities)

	Celecoxib 200 mg BID	Diclofenac SR 75 mg BID + Omeprazole 20 mg QD
	n (%)	n (%)
Musculoskeletal and connective tissue disorders	7 (0.3)	11 (0.5)
Back pain	1	1
Bone pain	0	1
Chondropathy	1	0
Intervertebral disc protrusion	1	1
Muscular weakness	0	1
Myalgia	0	1
Osteoarthritis	4 (0.2)	4 (0.2)
Rheumatoid arthritis	0	1
Rotator cuff syndrome	0	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	5 (0.2)	6 (0.3)
Adenocarcinoma	0	1
Basal cell carcinoma	0	1
Brain neoplasm	1	0
Breast cancer	0	1
Colon cancer	1	0
Endometrial cancer	0	1
Gastric adenoma	0	1
Hepatic neoplasm malignant	0	1
Leukaemia	1	0
Non-Hodgkin’s lymphoma	1	0
Thyroid cancer	1	0
Nervous system disorders	8 (0.4)	5 (0.2)
Balance disorder	1	0
Carotid artery stenosis	0	1
Cerebral haemorrhage	1	0
Cerebrovascular accident	1	2 (0.1)
Dizziness	0	2 (0.1)
Dysarthria	1	0
Facial palsy	1	0
Headache	1	1
Hypoaesthesia	1	1
Ischaemic stroke	0	2 (0.1)
Sciatica	1	0
Transient ischaemic attack	2 (0.1)	0
Psychiatric disorders	2 (0.1)	0
Major depression	1	0
Suicide attempt	1	0
Renal and urinary disorders	0	4 (0.2)
Calculus urinary	0	1
Haematuria	0	1
Renal failure	0	1
Renal failure acute	0	1
Tubulointerstitial nephritis	0	1
Reproductive system and breast disorders	1	1

Table 20. Treatment-Emergent Serious Adverse Events by Special Organ Class and Preferred Term (All Causalities)

	Celecoxib 200 mg BID	Diclofenac SR 75 mg BID + Omeprazole 20 mg QD
	n (%)	n (%)
Ovarian cyst	0	1
Ovarian cyst ruptured	1	0
Respiratory, thoracic and mediastinal disorders	4 (0.2)	5 (0.2)
Acute respiratory distress syndrome	1	0
Acute respiratory failure	1	0
Bronchitis chronic	0	1
Dyspnoea exertional	0	1
Interstitial lung disease	0	1
Nasal congestion	0	1
Pneumothorax	0	1
Pulmonary embolism	2 (0.1)	0
Skin and subcutaneous tissue disorders	1	0
Hypoaesthesia facial	1	0
Surgical and medical procedures	3 (0.1)	1
Carpal tunnel decompression	1	0
Hip arthroplasty	1	0
Open reduction of fracture	1	0
Prolapse repair	1	0
Rectocele repair	0	1
Vascular disorders	3 (0.1)	1
Deep vein thrombosis	1	0
Embolism	1	0
Hypertension	0	1
Thrombophlebitis superficial	1	0

Subjects were only counted once per treatment for each row.
Included data up to 30 days after last dose of study drug.
MedDRA (v12.0) coding dictionary applied.
BID = twice daily; MedDRA = Medical Dictionary for Regulatory Activities; QD = once daily; SR = slow release.

SAEs that were considered to be treatment-related are presented in Table 21 (note: this table is derived from the safety database and so the number of subjects with SAEs is different from Table 17, which is derived from the clinical database).

Table 21. Summary of Treatment-Related Serious Adverse Events

S. No.	Onset Day	Preferred Term	Sponsor/Investigator Causality	Outcome
Celecoxib				
1	254	Coronary artery disease	Related/Related	Recovered/Resolved
2	82	Transient ischemic attack	Related/Related	Not recovered/Not resolved
3	113	Pulmonary embolism	Related/Related	Fatal
	114	Cardiogenic shock	Related/Unrelated	Fatal
4	223	Cardiac failure	Related/Related	Recovered/Resolved with sequel
	223	Angina pectoris	Related/Related	Recovered/Resolved with sequel
5	164	Duodenal ulcer hemorrhage	Related/Related	Recovering/Resolving
6	174	Gastrointestinal hemorrhage	Related/Related	Recovered/Resolved
	174	Gastric ulcer	Related/Related	Unknown
	174	Erosive esophagitis	Related/Related	Unknown
	179	Deep vein thrombosis	Related/Related	Recovered/Resolved with sequel
	174	Duodenal ulcer	Related/Related	Unknown
7	122	Colitis	Related/Related	Recovered/Resolved
8	22	Thrombophlebitis superficial	Related/Related	Recovered/Resolved
9	62	Dysarthria	Related/Related	Recovered/Resolved
	63	Headache	Related/Related	Recovered/Resolved
	62	Nausea	Related/Related	Recovered/Resolved
10	58	Acute myocardial infarction	Related/Related	Recovered/Resolved
11	34	Gastric ulcer	Related/Related	Recovered/Resolved
12	57	Acute myocardial infarction	Related/Related	Recovered/Resolved
13	17	Cerebral hemorrhage	Related/Related	Recovered/Resolved with sequel
14	6	Chest pain	Related/Related	Recovered/Resolved
15	5	Cerebrovascular accident	Related/Related	Recovered/Resolved with sequel
16	129	Arrhythmia	Related/Related	Recovering/Resolving
Diclofenac and Omeprazole				
1	36	Gastritis erosive	Related/Related	Recovered/Resolved
2	14	Gastric ulcer	Unrelated/Related	Recovered/Resolved
	14	Nausea	Unrelated/Related	Recovered/Resolved
3	52	Cerebrovascular accident	Related/Related	Recovered/Resolved with sequel
	40	Dyspepsia	Related/Related	Recovered/Resolved
4	133	Gastric ulcer hemorrhage	Related/Related	Recovered/Resolved
5	52	Tubulointerstitial nephritis	Related/Related	Recovered/Resolved
	52	Normochromic normocytic anemia	Related/Related	Recovered/Resolved
6	159	Gastric ulcer	Related/Related	Not recovered/Not resolved
7	57	Acute myocardial infarction	Related/Related	Recovered/Resolved
8	161	Death	Related/Unrelated	Fatal
9	18	Cerebrovascular accident	Related/Related	Recovered/Resolved with sequel

Permanent Discontinuations Due to AEs: AEs that contributed to the withdrawal of subjects are summarized in Table 22.

Table 22. Summary of Adverse Events Most Frequently Contributing to Discontinuation from Study – Safety Population

Number of Subjects (% of Discontinued Subjects) Discontinuing due to Adverse Event	Celecoxib 200 mg BID (N=2223)	Diclofenac SR 75 mg BID + Omeprazole 20 mg QD (N=2237)
Abdominal discomfort	5 (2.1%)	4 (1.2%)
Abdominal distension	0 (0.0%)	6 (1.8%)
Abdominal pain	14 (5.8%)	14 (4.1%)
Abdominal pain lower	0 (0.0%)	3 (0.9%)
Abdominal pain upper	14 (5.8%)	30 (8.9%)
Abdominal tenderness	0 (0.0%)	1 (0.3%)
Acute myocardial infarction	2 (0.8%)	1 (0.3%)
Acute respiratory distress syndrome	1 (0.4%)	0 (0.0%)
Acute sinusitis	2 (0.8%)	0 (0.0%)
Alanine aminotransferase increased	0 (0.0%)	11 (3.3%)
Anaemia	6 (2.5%)	26 (7.7%)
Angioedema	0 (0.0%)	1 (0.3%)
Anorexia	0 (0.0%)	4 (1.2%)
Aphthous stomatitis	1 (0.4%)	2 (0.6%)
Appendicitis	1 (0.4%)	0 (0.0%)
Arrhythmia	1 (0.4%)	0 (0.0%)
Arthralgia	5 (2.1%)	1 (0.3%)
Arthritis	2 (0.8%)	1 (0.3%)
Arthritis bacterial	0 (0.0%)	1 (0.3%)
Aspartate aminotransferase increased	0 (0.0%)	5 (1.5%)
Atrial fibrillation	0 (0.0%)	1 (0.3%)
Back pain	1 (0.4%)	0 (0.0%)
Balance disorder	1 (0.4%)	0 (0.0%)
Biliary tract dilation procedure	0 (0.0%)	1 (0.3%)
Bladder obstruction	0 (0.0%)	1 (0.3%)
Blood creatine increased	1 (0.4%)	0 (0.0%)
Blood creatinine increased	1 (0.4%)	2 (0.6%)
Blood glucose increased	0 (0.0%)	1 (0.3%)
Blood potassium abnormal	0 (0.0%)	1 (0.3%)
Blood pressure increased	2 (0.8%)	0 (0.0%)
Blood urea increased	2 (0.8%)	3 (0.9%)
Breast cancer	0 (0.0%)	1 (0.3%)
Bronchopneumonia	0 (0.0%)	1 (0.3%)
Calculus urinary	0 (0.0%)	1 (0.3%)
Cerebral haemorrhage	2 (0.8%)	0 (0.0%)
Cerebrovascular accident	2 (0.8%)	3 (0.9%)
Chest pain	5 (2.1%)	3 (0.9%)
Cholecystitis	0 (0.0%)	1 (0.3%)
Cholelithiasis	0 (0.0%)	1 (0.3%)
Chondropathy	2 (0.8%)	0 (0.0%)
Colitis	0 (0.0%)	1 (0.3%)
Confusional state	1 (0.4%)	0 (0.0%)
Constipation	0 (0.0%)	5 (1.5%)
Coronary artery stenosis	1 (0.4%)	0 (0.0%)
Cough	5 (2.1%)	0 (0.0%)
Cystitis	0 (0.0%)	1 (0.3%)
Defaecation urgency	0 (0.0%)	1 (0.3%)
Dermatitis	0 (0.0%)	1 (0.3%)
Dermatitis allergic	4 (1.7%)	1 (0.3%)

Table 22. Summary of Adverse Events Most Frequently Contributing to Discontinuation from Study – Safety Population

Number of Subjects (% of Discontinued Subjects) Discontinuing due to Adverse Event	Celecoxib 200 mg BID (N=2223)	Diclofenac SR 75 mg BID + Omeprazole 20 mg QD (N=2237)
Dermatitis contact	1 (0.4%)	0 (0.0%)
Diarrhoea	15 (6.2%)	27 (8.0%)
Diplopia	0 (0.0%)	1 (0.3%)
Discomfort	1 (0.4%)	0 (0.0%)
Diverticulum intestinal	0 (0.0%)	2 (0.6%)
Dizziness	4 (1.7%)	5 (1.5%)
Drug eruption	1 (0.4%)	0 (0.0%)
Drug hypersensitivity	1 (0.4%)	2 (0.6%)
Drug intolerance	1 (0.4%)	0 (0.0%)
Dry mouth	1 (0.4%)	0 (0.0%)
Duodenal ulcer	3 (1.2%)	3 (0.9%)
Duodenitis	0 (0.0%)	2 (0.6%)
Duodenogastric reflux	0 (0.0%)	1 (0.3%)
Dysentery	0 (0.0%)	1 (0.3%)
Dysgeusia	1 (0.4%)	0 (0.0%)
Dyspepsia	32 (13.2%)	21 (6.2%)
Dyspnoea	2 (0.8%)	1 (0.3%)
Dyspnoea exertional	0 (0.0%)	1 (0.3%)
Eczema	1 (0.4%)	0 (0.0%)
Embolism	1 (0.4%)	0 (0.0%)
Endometrial cancer	1 (0.4%)	1 (0.3%)
Enteritis	1 (0.4%)	2 (0.6%)
Enterocolitis infectious	0 (0.0%)	1 (0.3%)
Epigastric discomfort	1 (0.4%)	2 (0.6%)
Erosive oesophagitis	2 (0.8%)	0 (0.0%)
Erythema nodosum	1 (0.4%)	0 (0.0%)
Extremity necrosis	0 (0.0%)	1 (0.3%)
Eyelid oedema	1 (0.4%)	2 (0.6%)
Face oedema	0 (0.0%)	2 (0.6%)
Fall	0 (0.0%)	1 (0.3%)
Fatigue	0 (0.0%)	1 (0.3%)
Flatulence	1 (0.4%)	1 (0.3%)
Frequent bowel movements	0 (0.0%)	1 (0.3%)
Gamma-glutamyltransferase increased	0 (0.0%)	8 (2.4%)
Gastric adenoma	0 (0.0%)	2 (0.6%)
Gastric disorder	0 (0.0%)	3 (0.9%)
Gastric haemorrhage	0 (0.0%)	1 (0.3%)
Gastric polyps	0 (0.0%)	1 (0.3%)
Gastric ulcer	6 (2.5%)	20 (5.9%)
Gastric ulcer haemorrhage	0 (0.0%)	1 (0.3%)
Gastritis	15 (6.2%)	17 (5.0%)
Gastritis atrophic	1 (0.4%)	0 (0.0%)
Gastritis erosive	4 (1.7%)	21 (6.2%)
Gastritis haemorrhagic	1 (0.4%)	1 (0.3%)
Gastroenteritis	1 (0.4%)	0 (0.0%)
Gastrointestinal disorder	0 (0.0%)	1 (0.3%)
Gastrointestinal erosion	0 (0.0%)	1 (0.3%)
Gastrointestinal haemorrhage	1 (0.4%)	4 (1.2%)
Gastrointestinal pain	1 (0.4%)	0 (0.0%)

Table 22. Summary of Adverse Events Most Frequently Contributing to Discontinuation from Study – Safety Population

Number of Subjects (% of Discontinued Subjects) Discontinuing due to Adverse Event	Celecoxib 200 mg BID (N=2223)	Diclofenac SR 75 mg BID + Omeprazole 20 mg QD (N=2237)
Gastrooesophageal reflux disease	4 (1.7%)	2 (0.6%)
Generalised oedema	0 (0.0%)	2 (0.6%)
Gout	0 (0.0%)	1 (0.3%)
Haematochezia	0 (0.0%)	5 (1.5%)
Haematocrit decreased	4 (1.7%)	13 (3.8%)
Haematocrit increased	0 (0.0%)	1 (0.3%)
Haematuria	0 (0.0%)	3 (0.9%)
Haemoglobin	0 (0.0%)	1 (0.3%)
Haemoglobin decreased	21 (8.7%)	39 (11.5%)
Haemorrhagic erosive gastritis	0 (0.0%)	1 (0.3%)
Haemorrhoids	0 (0.0%)	2 (0.6%)
Headache	3 (1.2%)	5 (1.5%)
Helicobacter infection	2 (0.8%)	0 (0.0%)
Helicobacter pylori identification test posit	2 (0.8%)	0 (0.0%)
Hepatic enzyme increased	0 (0.0%)	5 (1.5%)
Hepatitis	0 (0.0%)	2 (0.6%)
Hiatus hernia	3 (1.2%)	1 (0.3%)
Hip arthroplasty	1 (0.4%)	0 (0.0%)
Hyperhidrosis	1 (0.4%)	3 (0.9%)
Hyperkalaemia	0 (0.0%)	1 (0.3%)
Hypersensitivity	2 (0.8%)	0 (0.0%)
Hypertension	10 (4.1%)	9 (2.7%)
Hypertensive crisis	2 (0.8%)	2 (0.6%)
Hypertrophic anal papilla	0 (0.0%)	1 (0.3%)
Hypoaesthesia	1 (0.4%)	0 (0.0%)
Hypoaesthesia facial	1 (0.4%)	0 (0.0%)
Ileal ulcer	0 (0.0%)	2 (0.6%)
Impaired gastric emptying	1 (0.4%)	0 (0.0%)
Insomnia	0 (0.0%)	1 (0.3%)
Intervertebral disc protrusion	2 (0.8%)	0 (0.0%)
Irritable bowel syndrome	0 (0.0%)	1 (0.3%)
Ischaemic stroke	0 (0.0%)	1 (0.3%)
Joint effusion	0 (0.0%)	1 (0.3%)
Leukaemia	1 (0.4%)	0 (0.0%)
Leukocytosis	1 (0.4%)	0 (0.0%)
Leukopenia	1 (0.4%)	0 (0.0%)
Lip oedema	0 (0.0%)	1 (0.3%)
Liver disorder	1 (0.4%)	1 (0.3%)
Liver function test abnormal	0 (0.0%)	1 (0.3%)
Malaise	1 (0.4%)	0 (0.0%)
Medical device complication	0 (0.0%)	1 (0.3%)
Melaena	1 (0.4%)	0 (0.0%)
Metaplasia	1 (0.4%)	0 (0.0%)
Mouth ulceration	3 (1.2%)	0 (0.0%)
Multiple allergies	0 (0.0%)	1 (0.3%)
Muscle spasms	0 (0.0%)	1 (0.3%)
Muscular weakness	0 (0.0%)	1 (0.3%)
Musculoskeletal pain	1 (0.4%)	1 (0.3%)

Table 22. Summary of Adverse Events Most Frequently Contributing to Discontinuation from Study – Safety Population

Number of Subjects (% of Discontinued Subjects) Discontinuing due to Adverse Event	Celecoxib 200 mg BID (N=2223)	Diclofenac SR 75 mg BID + Omeprazole 20 mg QD (N=2237)
Myalgia	1 (0.4%)	2 (0.6%)
Myocardial infarction	1 (0.4%)	0 (0.0%)
Nausea	9 (3.7%)	18 (5.3%)
Neck pain	1 (0.4%)	0 (0.0%)
Nephrotic syndrome	0 (0.0%)	1 (0.3%)
Nervousness	0 (0.0%)	1 (0.3%)
Non-Hodgkin's lymphoma	1 (0.4%)	0 (0.0%)
Normochromic normocytic anaemia	0 (0.0%)	2 (0.6%)
Occult blood	2 (0.8%)	1 (0.3%)
Occult blood positive	1 (0.4%)	4 (1.2%)
Oedema	1 (0.4%)	1 (0.3%)
Oedema peripheral	5 (2.1%)	8 (2.4%)
Oesophageal ulcer	1 (0.4%)	0 (0.0%)
Oesophagitis	1 (0.4%)	2 (0.6%)
Oliguria	0 (0.0%)	1 (0.3%)
Osteoarthritis	3 (1.2%)	5 (1.5%)
Pain	1 (0.4%)	0 (0.0%)
Pain in extremity	2 (0.8%)	0 (0.0%)
Paraesthesia	1 (0.4%)	0 (0.0%)
Periorbital oedema	1 (0.4%)	0 (0.0%)
Pneumonia	0 (0.0%)	2 (0.6%)
Polymyalgia rheumatica	0 (0.0%)	1 (0.3%)
Prolapse repair	1 (0.4%)	0 (0.0%)
Prurigo	0 (0.0%)	1 (0.3%)
Pruritus	0 (0.0%)	2 (0.6%)
Pulmonary embolism	1 (0.4%)	0 (0.0%)
Pulmonary tuberculosis	2 (0.8%)	0 (0.0%)
Pyrexia	4 (1.7%)	1 (0.3%)
Rash	5 (2.1%)	2 (0.6%)
Rectal haemorrhage	1 (0.4%)	0 (0.0%)
Reflux oesophagitis	1 (0.4%)	2 (0.6%)
Renal failure	2 (0.8%)	0 (0.0%)
Renal failure acute	1 (0.4%)	2 (0.6%)
Renal impairment	1 (0.4%)	1 (0.3%)
Retinal vein occlusion	1 (0.4%)	0 (0.0%)
Rheumatoid arthritis	0 (0.0%)	3 (0.9%)
Rosacea	1 (0.4%)	0 (0.0%)
Rotator cuff syndrome	1 (0.4%)	0 (0.0%)
Sciatica	2 (0.8%)	2 (0.6%)
Skin reaction	0 (0.0%)	1 (0.3%)
Somnolence	1 (0.4%)	0 (0.0%)
Swelling face	0 (0.0%)	1 (0.3%)
Thrombophlebitis superficial	2 (0.8%)	0 (0.0%)
Thyroid cancer	1 (0.4%)	0 (0.0%)
Tinnitus	1 (0.4%)	0 (0.0%)
Tongue disorder	0 (0.0%)	1 (0.3%)
Tongue oedema	0 (0.0%)	1 (0.3%)
Transaminases increased	0 (0.0%)	7 (2.1%)
Transient ischaemic attack	1 (0.4%)	2 (0.6%)

Table 22. Summary of Adverse Events Most Frequently Contributing to Discontinuation from Study – Safety Population

Number of Subjects (% of Discontinued Subjects) Discontinuing due to Adverse Event	Celecoxib 200 mg BID (N=2223)	Diclofenac SR 75 mg BID + Omeprazole 20 mg QD (N=2237)
Traumatic brain injury	0 (0.0%)	2 (0.6%)
Tubulointerstitial nephritis	0 (0.0%)	2 (0.6%)
Upper gastrointestinal haemorrhage	1 (0.4%)	0 (0.0%)
Urinary tract infection	1 (0.4%)	0 (0.0%)
Urticaria	2 (0.8%)	4 (1.2%)
Varicose vein	1 (0.4%)	0 (0.0%)
Vertigo	2 (0.8%)	1 (0.3%)
Vertigo positional	1 (0.4%)	0 (0.0%)
Vomiting	5 (2.1%)	6 (1.8%)

BID = twice daily; QD = once daily; SR = slow release.
Percentages for each preferred term use the number of subjects discontinued due to adverse events as the denominator.

The number of subjects with dose reductions and/or temporary discontinuations due to AEs was 130 subjects (5.8%) in the celecoxib group and 210 subjects (9.4%) in the diclofenac and omeprazole group.

Deaths: There were a total of 6 deaths: 2 deaths in the celecoxib group and 4 deaths in the diclofenac and omeprazole group (Table 23). One subject in each group died due to SAEs that were considered to be related to treatment by the sponsor: 1 subject in the celecoxib group (pulmonary embolism and cardiogenic shock) and another in the diclofenac and omeprazole group (death); however, of these 3 SAEs, only the pulmonary embolism was considered to be treatment-related by the investigator.

Table 23. Summary of Deaths

S.No.	Cause of Death	Day of Death	Sponsor/ Investigator Causality
Celecoxib			
1	Pulmonary embolism	114	Related/Related
	Cardiogenic shock	114	Related/Unrelated
2	Bronchopneumonia	130	Unrelated/Unrelated
Diclofenac and Omeprazole			
3	Cardiac arrest[a]	123	Unrelated/Unrelated
4	Cardiogenic shock	355	Unrelated/Unrelated
5	Hepatic neoplasm malignant	675	Unrelated/Unrelated
6	Death	161	Related/Unrelated

a. Case was sent to the cardiovascular (CV) committee for adjudication and it was determined that this was a non-CV event.

CONCLUSIONS:

- There were 20/2238 subjects (0.9%) in the celecoxib group and 81/2246 subjects (3.6%) in the diclofenac and omeprazole group who were adjudicated as having CSULGIEs. The incidence of CSULGIEs was significantly lower for the celecoxib group compared to the diclofenac and omeprazole group. The incidence of CSULGIEs or SUs was also significantly lower for the celecoxib group.

- Overall, there was no significant treatment difference in terms of the changes from baseline in the Patient's Global Arthritis Assessment.

- There were more marked mean decreases in Hb and Hct for the diclofenac and omeprazole group compared to the celecoxib group, and the proportion of subjects with a clinically significant decrease in Hb and/or Hct was significantly greater for the diclofenac and omeprazole group compared to the celecoxib group.

- Post-baseline, the number of subjects with GGT or ALT ≥3 x ULN was significantly greater for the diclofenac and omeprazole compared to the celecoxib group. The number of subjects with post-baseline AST ≥3 x ULN was similar for both treatment groups. Overall, there was a mean decrease compared to baseline in the hepatic measures (GGT, ALT and AST) for the celecoxib group compared to a mean increase for the diclofenac and omeprazole group; this treatment difference was statistically significant.

- The proportion of subjects with moderate to severe abdominal symptoms and the proportion of subjects withdrawn due to GI AEs were significantly greater for the diclofenac and omeprazole group compared to the celecoxib group.

- There were no significant treatment differences for changes from baseline in iron binding capacity, ferritin or CRP.

- Treatment-related AEs were reported for 25.3% and 32.9% of subjects in the celecoxib group and the diclofenac and omeprazole group, respectively. The proportion of subjects reporting SAEs was <3% for both groups (with <1% in each group reporting treatment-related SAEs).

- In terms of body system, GI disorders were the most frequently reported AEs, and these were more common in subjects in the diclofenac and omeprazole group. The most common AEs were dyspepsia and diarrhea.

- The proportion of subjects who discontinued due to AEs was higher for the diclofenac and omeprazole group (15.1%) compared to the celecoxib group (10.9%).

- In the celecoxib group, 6 subjects (0.3%) had events adjudicated as primary CV endpoints (Antiplatelet Trialists' Collaboration [APTC] - CV death, myocardial infarction, or stroke) compared to 5 subjects (0.2%) in the diclofenac and omeprazole group. Eight subjects (0.4%) had events adjudicated as secondary CV endpoints in the celecoxib group compared to 1 subject (<0.1%) in the diclofenac and omeprazole group.

The difference in the secondary CV endpoints was driven mainly by differences in CV events adjudicated to be venous and peripheral vascular thrombotic events.