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

THERAPEUTIC AREA AND FDA APPROVED INDICATIONS: See United States Package Insert (USPI).

NATIONAL CLINICAL TRIAL NO.: NCT00549549

PROTOCOL NO.: A3191219

PROTOCOL TITLE: A Phase 3, Randomized, Double-Blind, Multi-Center, Active Controlled Trial to Evaluate the Efficacy and Safety of Celecoxib (Celebrex®) and Indomethacin in the Treatment of Moderate to Severe Acute Gouty Arthritis

Study Centers: This study was conducted at a total of 100 centers (including 25 centers that did not randomize subjects) in the following countries: Canada (10 centers, including 1 center that did not randomize subjects), Colombia (3 centers, including 1 center that did not randomize subjects), Costa Rica (4 centers, including 2 centers that did not randomize subjects), Italy (3 centers, none of which randomized subjects), Mexico (4 centers, including 1 center that did not randomize subjects), Peru (3 centers), Philippines (7 centers, including 1 center that did not randomize subjects), Republic of Korea (3 centers, including 1 center that did not randomize subjects), Russian Federation (4 centers), Spain (3 centers, including 2 centers that did not randomize subjects), Taiwan (3 centers), Thailand (2 centers), and United States (51 centers, including 13 centers that did not randomize subjects).

Study Initiation and Completion Dates: 26 February 2008 to 18 December 2009

Phase of Development: Phase 3

Study Objectives: The primary objective of this study was to demonstrate the superior analgesic efficacy of the celecoxib 800/400 mg regimen compared to the celecoxib 50 mg twice daily (BID), in the treatment of subjects with moderate to extreme pain due to acute gouty arthritis.

The secondary objectives of this study were to evaluate:

- The anti-inflammatory effects of celecoxib (celecoxib 800/400 mg and 400/200 mg regimens compared to celecoxib 50 mg BID) in the treatment of subjects with moderate to extreme pain due to acute gouty arthritis;

- Analgesic efficacy of celecoxib 400/200 mg regimen compared to celecoxib 50 mg BID in the treatment of subjects with moderate to extreme pain due to acute gouty arthritis;

- Analgesic efficacy and anti-inflammatory effects of 3 celecoxib dosage regimens compared to indomethacin in subjects with moderate to extreme pain due to an acute gouty arthritis;

- Safety and tolerability of celecoxib in subjects with moderate to extreme pain due to acute gouty arthritis.

METHODS

Study Design: This was a multi-center, double-blind, double-dummy, randomized, active-controlled study that included an 8-day treatment period followed by a 1-week follow-up period in subjects experiencing signs and symptoms of an acute exacerbation of gouty arthritis. Approximately 400 subjects were to be randomized in a 1:1:1:1 ratio to 1 of 3 dosage regimens of celecoxib or to indomethacin. The treatment allocation was stratified for monoarticular or oligoarticular (2 to 4 joints involved) acute gouty arthritis.

Number of Subjects (Planned and Analyzed): A total of 400 subjects were planned and analyzed.

Diagnosis and Main Criteria for Inclusion: Subjects who were at least 18 years of age or older, had acute gouty arthritis meeting the American College of Rheumatology criteria for acute arthritis of primary gout, had onset of pain from an acute gouty arthritis attack within 48 hours prior to screening/baseline, had a rating of moderate, severe, or extreme (2, 3, or 4, respectively) on the Patient's Assessment of Pain Intensity (pain over the past 24 hours) in the index joint at screening/baseline, and who were a candidate for daily therapy with an nonsteroidal anti-inflammatory drug (NSAID) and/or analgesic, in the investigator's judgment. Subjects with diagnosis of any other type of arthritis, with acute polyarticular gout (involving greater than 4 joints) or chronic gout, or who had used any NSAID or analgesic therapy to treat the current acute gouty arthritis attack were excluded.

Study Treatment: Eligible subjects received 1 of the following treatments as described on the treatment blister card:

1. Initial dose of celecoxib 800 mg, followed by a second dose of 400 mg 12 hours later on Day 1 and continuing at 400 mg BID on Days 2-8 (celecoxib 800/400 mg regimen); or

2. Initial dose of celecoxib 400 mg, followed by a second dose of 200 mg 12 hours later on Day 1 and continuing at 200 mg BID on Days 2-8 (celecoxib 400/200 mg regimen); or

3. Celecoxib 50 mg BID on Days 1-8; or

4. Indomethacin 50 mg three times daily (TID) on Days 1-8.

Efficacy Evaluations: The primary efficacy endpoint was the change from baseline to Day 2 (24-hour recall of pain experienced during Day 2 assessed on the morning of Day 3) in the Patient's Assessment of Pain Intensity in the index joint.

The secondary efficacy endpoints were:

- Physician's assessment of the index joint on Day 5, Day 9 and on Day 14 (final visit/early termination): change from baseline to each post-baseline assessment for 'tenderness' and 'swelling', and incidence at each post-baseline assessment of 'redness' and 'warmth';

- Change from baseline to Days 1 to 13 in the Patient's Assessment of Pain Intensity (24-hour recall of pain experienced during prior day as assessed on the next morning for each day), and average change in this measure over Days 2-4, Days 2-8 and Days 2-13;

- Change from baseline in the Patient's Assessment of Pain Intensity at each of 2, 4, 8 and 12 hours post first dose of study drug on Day 1, and both prior to the first dose of study drug on Day 2 (approximately 24 hours after initiating study drug) and prior to the second dose of study drug on Day 2 (approximately 32 hours after initiating study drug);

- Time weighted average (TWA) change from baseline in the Patient's Assessment of Pain Intensity over 8 (TWA-8), 12 (TWA-12) and 24 (TWA-24) hours post first dose of study drug on Day 1;

- Incidence of at least a 30% and 50% reduction from baseline in the Patient's Assessment of Pain Intensity on Day 2 (24-hour recall of pain experienced during Day 2 assessed on the morning of Day 3);

- Percent change from baseline in the Patient's Assessment of Pain Intensity for the average pain intensity on Days 2-4, Days 2-8 and Days 2-13;

- Incidence of and time to withdrawal due to lack of efficacy on Day 1 and over Days 1-8;

- Patient's Global Evaluation of study medication score on Day 9.

Safety Evaluations: All observed or volunteered adverse events (AEs) regardless of treatment group or suspected causal relationship to the investigational products were reported. Gastrointestinal (GI) tolerability information and central nervous system (CNS) tolerability information were collected using reports of moderate or severe nausea, abdominal pain, and dyspepsia (for GI tolerability) and reports of moderate or severe headache, nausea, dizziness, vertigo, vomiting and somnolence (for CNS tolerability).

Clinical laboratory tests were performed at screening/baseline and Day 14.

Vital signs (sitting) were obtained at the screening/baseline, Day 9, and Day 14 (final/early termination) visits.

For Korean sites only, a 12-lead electrocardiogram was collected at screening/baseline and Day 14 ± 1 day final visit/early termination, and a fecal sample was collected for the fecal occult blood test at Day 14 ± 1 day (Visit 4) final visit/early termination.

Statistical Methods: The primary efficacy endpoint was analyzed using analysis of covariance (ANCOVA) with randomization stratum (2 levels: monoarticular or oligoarticular), region, and treatment group as factors, and the Patient's Assessment of Pain Intensity (for the prior 24 hours) at baseline as a covariate. This model was used to perform the primary comparison described above. Corresponding two-sided 95% confidence interval (CI) was calculated.

Secondary endpoints were analyzed in a similar fashion, with the exception of the binary endpoints (incidence of at least a 30% and 50% reduction from baseline in the Patient's Assessment of Pain Intensity on Day 2, Physician's assessment of the index joint for 'redness' and 'warmth', and incidence of withdrawal due to lack of efficacy on Day 1 and over Days 1-8), which were analyzed using the Cochran-Mantel-Haenszel test stratified by randomization stratum. The time to withdrawal due to lack of efficacy was analyzed using a log-rank test and summarized using a Kaplan-Meier plot.

RESULTS

Subject Disposition and Demography: A total of 443 subjects were screened, of which 402 subjects were assigned to treatment and 400 received treatment (Table 1). Two subjects assigned to treatment were not treated: 1 subject assigned to the celecoxib 800/400 mg group (insufficient drug quantity at site) and 1 subject assigned to the indomethacin 50 mg TID group (subject no longer willing to participate in study).

Overall, 314/400 subjects (78.5%) completed the study and 86/400 subjects (21.5%) discontinued. The percentage of subjects who completed was approximately 76%-78% for all groups except for celecoxib 800/400 mg, where 83.7% of subjects completed. Most of the discontinuations (59/86 subjects, 68.6%) were for reasons not related to study drug, primarily for reasons reported as 'other' (38/86 subjects, 44.2%).

Table 1. Subject Evaluation Groups

Number (%) of Subjects		Celecoxib 50 mg BID	Celecoxib 400/200 mg	Celecoxib 800/400 mg	Indomethacin 50 mg TID
Screened	443				
Assigned to Study Treatment		101	99	99	103
Treated		101	99	98	102
Completed		77 (76.2)	77 (77.8)	82 (83.7)	78 (76.5)
Discontinued		24 (23.8)	22 (22.2)	16 (16.3)	24 (23.5)
During active/double blind treatment[a]		23 (95.8)	19 (86.4)	14 (87.5)	20 (83.3)
During post-therapy follow-up[a]		1 (4.2)	3 (13.6)	2 (12.5)	4 (16.7)
Related to Study Drug		9 (8.9)	6 (6.1)	4 (4.1)	8 (7.8)
Adverse event		0	0	0	6 (5.9)
Lack of efficacy		9 (8.9)	6 (6.1)	4 (4.1)	2 (2.0)
Not Related to Study Drug		15 (14.9)	16 (16.2)	12 (12.2)	16 (15.7)
Adverse Event		5 (5.0)	3 (3.0)	1 (1.0)	3 (2.9)
Lost to follow-up		1 (1.0)	0	1 (1.0)	2 (2.0)
Other		9 (8.9)	9 (9.1)	9 (9.2)	11 (10.8)
No longer willing to participate		0	4 (4.0)	1 (1.0)	0
Analyzed for Safety					
Analyzed for adverse events		101 (100.0)	99 (100.0)	98 (100.0)	102 (100.0)
Analyzed for laboratory data		98 (97.0)	95 (96.0)	95 (96.9)	95 (93.1)

BID = twice daily, TID = three times daily
[a] Denominator for percentages is the overall number of discontinued subjects.

Overall, 366/400 subjects (91.5%) were male and 34/400 subjects (8.5%) were female (Table 2), with a similar split observed for the 4 treatment groups. Mean age was approximately 50 years for all groups, with the age for individual subjects ranging from 23-90 years. In each group, >50% of subjects were white. Mean weight and body mass index were similar for all treatment groups.

Table 2. Summary of Demographic Characteristics – Safety Population

	Celecoxib 50 mg BID (N=101)	Celecoxib 400/200 mg (N=99)	Celecoxib 800/400 mg (N=98)	Indomethacin 50 mg TID (N=102)
Sex, number of subjects				
Male	91	90	90	95
Female	10	9	8	7
Age, years, number (%) of subjects				
18-44	28 (27.7)	28 (28.3)	26 (26.5)	34 (33.3)
45-64	56 (55.4)	55 (55.6)	60 (61.2)	54 (52.9)
≥65	17 (16.8)	16 (16.2)	12 (12.2)	14 (13.7)
Mean (SD)	52.4 (11.9)	52.3 (12.0)	51.0 (11.3)	49.6 (12.7)
Range	28-80	25-90	26-79	23-76
Race, number (%) of subjects				
White	53 (52.5)	64 (64.6)	54 (55.1)	55 (53.9)
Black	11 (10.9)	3 (3.0)	10 (10.2)	9 (8.8)
Asian	22 (21.8)	18 (18.2)	19 (19.4)	19 (18.6)
Other	15 (14.9)	14 (14.1)	15 (15.3)	19 (18.6)
Weight, kg				
Mean (SD)	90.6 (21.6)	90.9 (19.2)	94.7 (25.7)	93.9 (22.2)
Range	48.1-163.7	56.6-140.6	54.0-193.7	45.9-158.7
N	99	97	98	102
Body Mass Index, kg/m^2				
Mean (SD)	30.2 (5.7)	30.3 (5.1)	31.2 (7.1)	30.6 (5.9)
Range	14.5-45.7	19.6-47.8	20.1-64.7	17.3-47.4
N	99	97	98	102

BID = twice daily; TID = three times daily; N = number of subjects; n = number of subjects with observation; SD = standard deviation.

All 400 subjects had a primary diagnosis of gouty arthritis. Overall, 310/400 subjects (77.5%) had monoarticular gouty arthritis and 90/400 subjects (22.5%) had oligoarticular gouty arthritis; a similar split was seen within each of the 4 treatment groups.

Efficacy Results: The primary efficacy endpoint was the change from baseline in the Patient's Assessment of Pain Intensity in the index joint on Day 2. The mean change from baseline was greater (ie, there was a greater reduction in pain) for the celecoxib 800/400 mg group compared to the celecoxib 50 mg BID group, and this difference was statistically significant (least squares [LS] mean difference = -0.46, p=0.0014) (Table 3). Although the change from baseline for celecoxib 400/200 mg was more marked than for celecoxib 50 mg BID (LS mean difference = -0.24), this difference was not statistically significant (p=0.0947). For celecoxib 50 mg BID and celecoxib 400/200 mg, the reduction in pain was less marked than for indomethacin, with statistically significant LS mean differences compared to indomethacin of 0.57 (p<0.0001) and 0.33 (p=0.0196), respectively. For

celecoxib 800/400 mg, however, the change from baseline was comparable to that seen for indomethacin, and the LS mean difference was not statistically significant.

Table 3. Change from Baseline to Day 2 in Patient's Assessment of Pain Intensity (24-hour Recall Assessed on Day 3, LOCF) – ITT Population

	Celecoxib 50 mg BID (N=100)	Celecoxib 400/200 mg (N=99)	Celecoxib 800/400 mg (N=96)	Indomethacin 50 mg TID (N=102)
Baseline				
Mean (SD)	3.03 (0.67)	2.73 (0.62)	2.84 (0.69)	2.83 (0.76)
Median	3.0	3.0	3.0	3.0
Range (minimum, maximum)	2.0, 4.0	2.0, 4.0	2.0, 4.0	2.0, 4.0
N	100	99	96	102
Day 2 (Change from Baseline)				
Mean (SD)	-1.14 (1.10)	-1.23 (0.97)	-1.51 (1.11)	-1.62 (0.97)
Median	-1.0	-1.0	-2.0	-2.0
Range (minimum, maximum)	-4.0, 1.0	-3.0, 1.0	-4.0, 1.0	-3.0, 1.0
N	97	96	94	98
Versus Celecoxib 50 mg BID				
LS Mean Difference (SE)		-0.24 (0.14)	-0.46 (0.14)	
95% CI		-0.52, 0.04	-0.74, -0.18	
p-value		0.0947	0.0014	
Versus Indomethacin 50 mg TID				
LS Mean Difference (SE)	0.57 (0.14)	0.33 (0.14)	0.11 (0.14)	
95% CI	0.29, 0.84	0.05, 0.60	-0.17, 0.39	
p-value	<0.0001	0.0196	0.4331	

LOCF = last observation carried forward; ITT = Intent to treat; BID = twice daily; TID = three times daily; N = number of subjects; SD = standard deviation; n = number of subjects with observation; LS = least squares; SE = standard error; CI = confidence interval.
Model - analysis of covariance (ANCOVA) with randomization stratum (2 levels: monoarticular [1] or oligoarticular [>1]), region and treatment group as factors, and the Patient's Assessment of Pain Intensity at Baseline as a covariate.
Patient's Pain Intensity categories: 0 = none, 1 = mild, 2 = moderate, 3 = severe, 4 = extreme.

For the physician's assessment of the index joint in terms of tenderness, there were no statistically significant differences in the changes from baseline in celecoxib 400/200 mg and celecoxib 800/400 mg compared to celecoxib 50 mg BID, except for on Day 14, in favor of the celecoxib 800/400 mg group. Changes from baseline for the 3 celecoxib groups were not significantly different to the indomethacin group except for the celecoxib 50 mg BID group on Day 5, in favor of the indomethacin group.

For the physician's assessment of the index joint in terms of swelling, there were no statistically significant differences in the changes from baseline in celecoxib 400/200 mg and celecoxib 800/400 mg compared to celecoxib 50 mg BID, except for on Day 14, in favor of the celecoxib 800/400 mg group. Changes from baseline for the 3 celecoxib groups were not significantly different to the indomethacin group.

For the physician's assessment of the index joint in terms of redness and warmth, there were no statistically significant treatment differences observed at any of the time points.

For the Patient's Assessment of Pain Intensity in the index joint, analysis of the daily scores showed that a significant difference between celecoxib 800/400 mg and celecoxib 50 mg BID was present on each day from Days 1-13, and between celecoxib 400/200 mg and celecoxib 50 mg on Day 1 and on Days 4-9. Celecoxib 50 mg BID was significantly different to indomethacin 50 mg TID on all days, with the exception of Days 12 and 13. Celecoxib 400/200 mg was also significantly different to indomethacin (in favor of indomethacin) on Day 2, but this only persisted until Day 5. Celecoxib 800/400 mg was not significantly different to indomethacin on any of Days 1-13.

When analyzed by time point on Days 1 and 2, celecoxib 400/200 mg was not significantly different to celecoxib 50 mg BID at any time point, but celecoxib 800/400 mg was significantly different to celecoxib 50 mg BID at all of these time points with the exception of the first; Day 1, 2 hours. Celecoxib 50 mg BID and 400/200 mg were significantly different to indomethacin for all Days 1 and 2 time points, with the exception of Day 2, 0 hours, where only celecoxib 50 mg BID was significantly different.

When compared to celecoxib 50 mg BID, celecoxib 800/400 mg was significantly different over all TWA periods, but celecoxib 400/200 mg was not. Both celecoxib 50 mg BID and 400/200 mg were significantly different to the indomethacin group over all TWA periods, while celecoxib 800/400 mg was not.

For the incidence of subjects with ≥30% and ≥50% reduction from baseline to Day 2 in Patient's Assessment of Pain Intensity, both the celecoxib 400/200 mg and 800/400 mg groups were significantly greater than the celecoxib 50 mg BID group. The incidence for the celecoxib 800/400 mg group was not significantly different to the indomethacin group, but the incidence was significantly lower than the indomethacin group for both celecoxib 50 mg BID and celecoxib 400/200 mg.

The incidence of withdrawal due to lack of efficacy was significantly greater for the celecoxib 50 mg BID group compared to the indomethacin group during treatment (10.0% compared to 2.9%, p=0.0213) and during the study (11.0% compared to 3.9%, p=0.0317).

For Patient's Global Evaluation of Study Medication, mean scores for the celecoxib 400/200 mg and 800/400 mg groups were not significantly different to either the celecoxib 50 mg BID or indomethacin groups. The mean score for celecoxib 50 mg BID (3.04) was lower than for indomethacin (3.33) and this difference was significant (LS mean difference = -0.26, p=0.0337).

Safety Results: For the 3 celecoxib treatment groups, the incidence of AEs (all causalities) ranged from 27.3%-32.7%, with the incidence being greater for the indomethacin group (43.1%) (Table 4). For treatment-related AEs, the incidence was lower for the celecoxib groups (9.2%-13.1%) compared to the indomethacin group (25.5%). Most AEs were mild or moderate in severity.

Table 4. Overall Summary of Adverse Events – Safety Population

Number (%) of Subjects	Celecoxib 50 mg BID	Celecoxib 400/200 mg	Celecoxib 800/400 mg	Indomethacin 50 mg TID
All Causalities				
Evaluable for AEs	101	99	98	102
Number of AEs	59	43	51	80
With AEs	33 (32.7)	27 (27.3)	28 (28.6)	44 (43.1)
With SAEs	0	0	0	1 (1.0)
With Severe AEs	5 (5.0)	3 (3.0)	2 (2.0)	1 (1.0)
Discontinued due to AEs	5 (5.0)	3 (3.0)	1 (1.0)	9 (8.8)
Dose Reduced or Temporary Discontinuations due to AEs	0	0	0	1 (1.0)
Treatment-Related				
Evaluable for AEs	101	99	98	102
Number of AEs	17	18	14	45
With AEs	10 (9.9)	13 (13.1)	9 (9.2)	26 (25.5)
With SAEs	0	0	0	0
With Severe AEs	1 (1.0)	1 (1.0)	1 (1.0)	0
Discontinued due to AEs	0	0	0	6 (5.9)
Dose Reduced or Temporary Discontinuations due to AEs	0	0	0	1 (1.0)

BID = twice daily; TID = three times daily; AE = adverse event; SAE = serious adverse event

With respect to preferred term, the most frequently reported AEs (all causalities) were gouty arthritis (20 subjects), headache (16 subjects), and gout (13 subjects) (Table 5). The incidence of these AEs was similar for the 4 treatment groups. With the exception of gouty arthritis for 1 subject in the celecoxib 400/200 mg group, episodes of gout or gouty arthritis were not considered to be related to treatment. The most frequently reported AE that was considered to be related to treatment was headache, reported by 3, 3, 3, and 2 subjects in the celecoxib 50 mg BID, celecoxib 400/200 mg, celecoxib 800/400 mg, and indomethacin 50 mg TID groups, respectively. Dizziness and abdominal pain upper were reported as treatment-related AEs by 6 and 5 subjects, respectively, in the indomethacin group but by no more than 1 subject in any of the celecoxib groups.

Table 5. Summary of Most Frequent Adverse Events (>2% of Subjects) by Preferred Term

	Celecoxib 50 mg BID (N=101)		Celecoxib 400/200 mg (N=99)		Celecoxib 800/400 mg (N=98)		Indomethacin 50 mg TID (N=102)	
Number (%) of Subjects	**AC**	**TR**	**AC**	**TR**	**AC**	**TR**	**AC**	**TR**
Gouty arthritis	4 (4.0)	0	7 (7.1)	1 (1.0)	3 (3.1)	0	6 (5.9)	0
Headache	5 (5.0)	3 (3.0)	4 (4.0)	3 (3.0)	3 (3.1)	2 (2.0)	4 (3.9)	2 (2.0)
Gout	2 (2.0)	0	2 (2.0)	0	6 (6.1)	0	3 (2.9)	0
Diarrhea	3 (3.0)	1 (1.0)	2 (2.0)	1 (1.0)	2 (2.0)	1 (1.0)	5 (4.9)	4 (3.9)
Dizziness	2 (2.0)	1 (1.0)	1 (1.0)	1 (1.0)	2 (2.0)	1 (1.0)	6 (5.9)	6 (5.9)
Arthralgia	1 (1.0)	1 (1.0)	4 (4.0)	0	3 (3.1)	0	2 (2.0)	0
Abdominal pain upper	1 (1.0)	0	0	0	1 (1.0)	1 (1.0)	5 (4.9)	5 (4.9)
Dyspepsia	2 (2.0)	1 (1.0)	0	0	2 (2.0)	2 (2.0)	3 (2.9)	2 (2.0)
Nausea	2 (2.0)	2 (2.0)	0	0	1 (1.0)	1 (1.0)	3 (2.9)	3 (2.9)
Pain in extremity	0	0	1 (1.0)	0	3 (3.1)	0	1 (1.0)	0
Pyrexia	4 (4.0)	0	1 (1.0)	0	0	0	0	0

BID = twice daily; TID = three times daily; N = number of subjects; AC = all causality, TR = treatment related. Table shows preferred terms where >2% of subjects in at least 1 group experienced an adverse event (all causalities).

There were no significant treatment differences observed in the incidence of moderate or severe GI or nervous system AEs.

The incidence of discontinuations due to AEs (all causalities) was greater for the indomethacin group (8.8%) compared to the celecoxib groups (1.0%-5.0%), and no subjects in the celecoxib groups discontinued due to treatment-related AEs compared to 6 subjects (5.9%) in the indomethacin group (Table 6).

Table 6. Discontinuations due to Treatment-Emergent Adverse Events

Sex/Age, years	MedDRA (v12.1) Preferred Term	Start/ Stop Day[a]	Severity	Outcome	Causality
Celecoxib 50 mg BID					
M/55	Gouty arthritis	11/>12	Moderate	Still present	Disease under study
M/63	Gouty arthritis	3/>3	Mild	Still present	Disease under study
M/77	Blood creatinine increased	1/>3	Moderate	Still present	Other – abnormal creatinine level
M/43	Joint effusion	2/3	Severe	Resolved	Disease under study
M/60	Osteoarthritis	2/13	Moderate	Resolved	Disease under study
Celecoxib 400/200 mg					
M/39	Gout	2/>8	Severe	Still present	Disease under study
M/58	Gouty arthritis	2/8	Moderate	Resolved	Disease under study
M/60	Gouty arthritis	9/10	Moderate	Resolved	Disease under study
Celecoxib 800/400 mg					
M/49	Gouty arthritis	12/>12	Moderate	Still present	Disease under study
Indomethacin 50 mg TID					
M/40	Gout	5/>5	Moderate	Still present	Disease under study
M/38	Fatigue	1/5	Moderate	Resolved	Study drug
M/76	Gout	3/>3	Moderate	Still present	Disease under study
M/34	Abdominal pain	3/>5	Moderate	Still present	Study drug
M/57	Pulmonary congestion	4/8	Mild	Resolved	Study drug
M/62	Pharyngotonsilitis	7/>9	Moderate	Still present	Other illness - pharyngoamigdalitis
M/51	Drug hypersensitivity	1/3	Mild	Resolved	Study drug
M/26	Dizziness	1/3	Mild	Resolved	Study drug
M/48	Angioedema	3/>5	Moderate	Still present	Study drug

MedDRA = Medical Dictionary for Regulatory Activities; M = male; BID = twice daily; TID = three times daily.
Age and weight were at screening
[a] Day relative to start of study treatment

There were no deaths. Only 1 subject reported a serious AE: this was in the indomethacin group (facial bones fracture) and was not considered to be related to treatment.

For the celecoxib 50 mg BID and 400/200 mg groups, there were median decreases of >10% of the baseline median for white blood cell count and total neutrophils (absolute). There were no median changes >10% for any other parameter, with the exception of a median decrease in monocytes (absolute) of 23% for the celecoxib 50 mg BID group.

Increases in sitting systolic blood pressure >30 mm Hg were reported for 1.0%, 0%, 1.1%, and 2.0% of subjects in the celecoxib 50 mg BID, celecoxib 400/200 mg, celecoxib 800/400 mg, and indomethacin 50 mg TID groups, respectively. No subjects had an increase in sitting diastolic blood pressure >30 mm Hg.

CONCLUSIONS:

- There was evidence of superior analgesic efficacy of the celecoxib 800/400 mg regimen compared to the celecoxib 50 mg BID, in the treatment of subjects with moderate to extreme pain due to acute gouty arthritis. For the primary endpoint, change from baseline to Day 2 (24-hour recall of pain experienced during Day 2 assessed on the morning of Day 3) in the Patient's Assessment of Pain Intensity, there was a reduction in pain compared to baseline for both treatments, with the difference between treatments being statistically significant (LS mean difference = -0.46, p=0.0014).

- For the Physician's Assessment of the Index Joint, on Day 14 significant differences were observed between celecoxib 800/400 mg compared to celecoxib 50 mg BID for tenderness (LS mean difference = -0.32, p=0.0036) and swelling (LS mean difference = -0.28, p=0.0226); differences were also observed on Days 5 and 9, although these were not significant. There was no significant difference between celecoxib 400/200 mg or 800/400 mg compared to celecoxib 50 mg BID in terms of the proportion of subjects with redness and warmth, with the exception of Day 14, where the percentage of subjects having warmth for the celecoxib 400/200 mg group was significantly lower than for the celecoxib 50 mg BID group.

- There was no significant treatment difference for celecoxib 400/200 mg compared to celecoxib 50 mg BID in change from baseline to Day 2 (24-hour recall of pain experienced during Day 2 assessed on the morning of Day 3) in the Patient's Assessment of Pain Intensity.

- The celecoxib 800/400 mg regimen had a change from baseline to Day 2 (24-hour recall of pain experienced during Day 2 assessed on the morning of Day 3) in the Patient's Assessment of Pain Intensity that was not significantly different to indomethacin 50 mg TID; for the other celecoxib regimens (400/200 mg and 50 mg BID), the reduction in pain observed was significantly less than that seen with indomethacin. Generally, there were no significant differences between any of the celecoxib regimens and indomethacin in terms of the Physician's Assessment of the Index Joint (tenderness, swelling, redness, and warmth).

- All 3 regimens of celecoxib and indomethacin were well tolerated; there were no deaths and no SAEs that were considered to be treatment-related. The incidence of AEs (all causalities or treatment-related) was lower for each of the celecoxib regimens compared to indomethacin.