

<p><i>These results are supplied for informational purposes only. Prescribing decisions should be made based on the approved package insert</i></p>		
<p>Link to drug label</p>		
<p><b>Proprietary Drug Name</b></p> <p>Celebrex</p>	<p><b>INN</b></p> <p>Celecoxib</p>	<p><b>Therapeutic area and FDA approved indications</b></p> <p>Relief of signs and symptoms of osteoarthritis Relief of signs and symptoms of rheumatoid arthritis in adults Management of acute pain in adults Treatment of primary dysmenorrhea Reduce the number of adenomatous colorectal polyps in familial adenomatous polyposis as an adjunct to usual care</p>
<p><b>Name of Sponsor/Company:</b> Pfizer Inc.</p>		
<p><b>Title of Study:</b> Protocol: A3191051 / N49-01-02-209 A study of the efficacy and tolerability of once daily Celebrex<sup>®</sup> (celecoxib) and twice daily naproxen vs placebo in the treatment of African American subjects with osteoarthritis of the knee</p>		
<p><b>Study centre(s):</b> 28 centers in the US</p>		
<p><b>Publication (reference, if applicable)</b> See attached bibliography</p>		
<p><b>Studied period</b> 31 Oct 2001 – 20 Nov 2002</p>		<p><b>Phase of development:</b> Phase 4</p>
<p><b>Objectives:</b> The primary objective of this study was to determine whether celecoxib, 200 mg taken once daily (<i>QD</i>), was as effective as naproxen, 500 mg taken twice daily (<i>BID</i>), in the treatment of symptoms associated with osteoarthritis (OA) of the knee. The secondary objective was to confirm the tolerability of celecoxib, 200 mg <i>QD</i>, versus placebo in African American subjects; the tertiary objective was to determine the use of complementary and alternative medicines in this population at Screening.</p>		
<p><b>Methodology:</b> This was a 6-week, multicenter, randomized, double-blind, placebo-controlled, active-comparator, parallel-group study in African American subjects with OA of the knee. Those with OA in a flare state and with a Functional Capacity Classification of I-III were eligible for study participation. Eligible subjects were randomized to 1 of 3 regimens, celecoxib 200 mg <i>QD</i>, naproxen 500 mg <i>BID</i>, or placebo, in a 2:2:1 ratio.</p> <p>The study included 4 clinic visits: Screening, Baseline, Week 2 and Week 6. Prior to enrollment, all subjects provided a complete medical and medication history. At Screening, subjects had an abbreviated physical examination, underwent clinical laboratory testing, and, if female of childbearing potential, received a urine pregnancy test (UPT). An evaluation of arthritis, consisting of both subject and physician assessments, was performed, and subjects completed a Patient Health Questionnaire and a Complementary and Alternative Medicines Questionnaire. Eligible subjects returned for the Baseline visit. Study medication and the American Pain Society (APS) Pain Measure diary were dispensed. In addition, subjects completed Baseline arthritis assessments and verification of flare criteria. Subjects were then stratified into 2 groups (based on a Baseline Assessment of Arthritis Pain visual analogue scale [VAS] <math>\leq 69</math> mm or <math>\geq 70</math> mm) and randomized to receive treatment. Use of analgesic medication, other than the study medication, for treatment of arthritis symptoms was prohibited throughout the study period. Subjects returned for the Week 2 visit for Week 2 arthritis assessments and to receive additional study medication.</p>		

At the Week 6 visit each subject completed the Week 6 arthritis assessments, the Pain Satisfaction Scale, and the Patient Health Questionnaire, and study medication was collected. Subjects had an abbreviated physical examination, underwent clinical laboratory testing, and, if female of childbearing potential, received a UPT. In addition, concomitant medication and adverse event (AE) information was recorded.

**Number of patients (planned and analyzed):** Planned enrollment was 300 randomized subjects in order to ensure a sufficient number of subjects eligible for the efficacy evaluable (PPA) population. Actual enrollment was 322 randomized subjects (127, 128, and 67 subjects in the celecoxib, naproxen, and placebo treatment groups, respectively). A total of 316 subjects were included in the safety population, 314 subjects were included in the modified intent-to-treat (MITT) population, and 252 subjects were included in the PPA population.

**Diagnosis and main criteria for inclusion:** Healthy African American subjects at least 45 years old with diagnosed OA of the knee in a flare state and with a Functional Capacity Classification of I-III were eligible for study participation. Subjects taking non-steroidal anti-inflammatory drug (NSAID) were required to discontinue medication at least 48 hours prior to the Baseline assessments. Subjects indicated an Assessment of Arthritis Pain VAS score between 40 and 90 mm and had a minimum rating of 3 (ie, fair – moderate symptoms and limitation of some normal activities) on the Physician's and Patient's Global Assessments of Arthritis at the Baseline visit.

**Duration of treatment:** 6 weeks

**Test product, dose and mode of administration:** Celecoxib treatment: Subjects randomized to the celecoxib treatment group were treated with 200 mg celecoxib *QD* for 6 weeks. They were instructed to take 2 capsules (consisting of 1 celecoxib 200 mg capsule and 1 placebo capsule identical to naproxen) daily with the morning meal and 1 capsule (consisting of 1 placebo capsule identical to naproxen) daily with the evening meal.

**Reference therapy, dose and mode of administration** Naproxen treatment: Subjects randomized to the naproxen treatment group were treated with naproxen 500 mg *BID* for 6 weeks. They were instructed to take 2 capsules (consisting of one 500 mg naproxen over-encapsulated tablet and 1 placebo capsule identical to celecoxib) daily with the morning meal and 1 capsule (consisting of one 500 mg naproxen over-encapsulated tablet) daily with the evening meal.

Placebo treatment: Subjects randomized to the placebo treatment group were treated with placebo for 6 weeks. They were instructed to take 2 capsules (consisting of 1 placebo capsule identical to celecoxib and 1 placebo capsule identical to naproxen) daily with the morning meal and 1 capsule (consisting of 1 placebo capsule identical to naproxen) daily with the evening meal. The placebos were similar in size, color, smell, taste and appearance to the study medications.

**Criteria for evaluation:** Efficacy: The primary efficacy variable was the change in the Patient's Assessment of Arthritis Pain at Week 6 compared to Baseline: Subjects assessed the severity of arthritis pain in their index joint using a VAS from 0 mm (no pain) to 100 mm (worst pain). Secondary efficacy variables were: change in Patient's and Physician's Global Assessments of Arthritis from Baseline to Week 6/Early Termination, change in Western Ontario and McMaster Universities (WOMAC) Osteoarthritis Index from Baseline to Week 6/Early Termination, change in APS pain scores from Baseline to Week 6/Early Termination, the Pain Satisfaction Scale, the Patient Health Questionnaire (PHQ-9), and measurement of Upper Gastrointestinal (UGI) Tolerability. The tertiary efficacy variable was the Complementary and Alternative Questionnaire Worksheet completed at the Screening visit.

Safety: General clinical safety was assessed by the monitoring of treatment-emergent AEs and the results of physical examination.

**Statistical methods:** The primary analysis population was the PPA population which included all treated subjects with 70% to 120% treatment compliance, without major protocol violations and with both Baseline and Week 6 VAS assessments.

The change in the VAS score (Week 6 – Baseline) was analyzed using a general linear model with treatment

and center effects in the model, and Baseline score as a covariate. Pairwise comparisons were conducted. Celecoxib was declared as effective as naproxen if the lower bound of the 2-sided 95% confidence interval of the treatment difference (naproxen – celecoxib) lay above -10 mm. As a test of internal control, the primary efficacy parameter was also tested for the differences between celecoxib vs placebo and naproxen vs placebo, with respect to mean change from Baseline. For the internal control, p-values, differences in the least-squares mean, standard errors of the differences and the 95% confidence interval for the differences were presented.

All secondary analyses were performed using the MITT population.

The 24-item WOMAC scale and subscales were analyzed using a general linear model with treatment and center effects in the model, and Baseline WOMAC score as a covariate.

For the Global Assessment (Patient’s and Physician’s) subjects were analyzed as “improved”, “no change”, or “worsened” using the Cochran-Mantel-Haenszel (CMH) test (row-mean-score-test), stratified by center.

APS questions were analyzed using the CMH test stratified by center (question 1, “yes” or “no”) or a general linear model with treatment, center, and Baseline value (questions 2-5) as a covariate.

The incidence of UGI events was analyzed using 2-tailed Fisher’s exact tests.

For the Patient Health Questionnaire, continuous variables were analyzed using the general linear model approach with treatment and center effect in the model and the Screening value as a covariate. For categorical variables, the CMH test was done using center as a stratification variable.

**Summary**

**EFFICACY RESULTS:**

Primary Efficacy: The following table summarizes the change in the Patient Assessment of Arthritis VAS scores.

	<b>Celecoxib</b>	<b>Naproxen</b>	<b>Placebo</b>
<b>Baseline</b>			
N	100	106	46
Mean	67.7	68.0	70.0
SE Mean	1.2	1.3	1.8
<b>Week 6</b>			
N	100	106	46
Mean	31.5	29.9	36.5
SE Mean	2.4	2.4	4.2
<b>Change from Baseline</b>			
N	100	106	46
LS Mean	-36.2	-38.0	-33.5
SE	2.7	2.5	4.2
	<b>Naproxen-Celecoxib</b>	<b>Naproxen-Placebo</b>	<b>Celecoxib-Placebo</b>
LS Mean	-2.2	-5.5	-3.3
SE	3.4	4.3	4.3
95% CI	[-8.9,4.4]	[-14.0,2.9]	[-11.7,5.2]
p-value	0.5060	0.1988	0.4459

The celecoxib treatment was observed to be as effective as naproxen according to the criteria specified in the protocol, since the lower bound of the 2-sided 95% CI of the treatment difference (naproxen-celecoxib) was above -10 mm (-8.9 mm). However, the placebo treatment group did not show a statistically significant difference from either active treatment.

Secondary Efficacy: The results for the secondary efficacy endpoints were similar between the active treatments. The Patient’s and Physician’s Global Assessment of Arthritis, the WOMAC OA Index scores, the Pain Satisfaction Scale and the Patient Health Questionnaire all showed no statistically significant differences between celecoxib and naproxen treatment groups, with the exception of 2 isolated occurrences: a significantly greater percentage of subjects in the naproxen group (76%) compared to the celecoxib group (64%) agreed or somewhat agreed that their pain medication affected their health positively (p=0.038), and significantly fewer subjects in the naproxen group compared to the celecoxib group were bothered by changes in appetite (p=0.0316). In general, OA pain was shown to decrease with therapy, however, there

were few indications of significant differences between active treatment and placebo.

Subjects in the celecoxib group had significantly fewer UGI events than subjects in both the naproxen and placebo groups (see Safety Results).

#### SAFETY RESULTS

The incidence of AEs and treatment-related AEs was similar among the treatment groups. The majority of AEs were moderate or mild in severity. The AEs in each treatment group were mainly GI system or psychiatric disorders. Among the AEs, only depression and headache occurred in >5% of the subject population.

A total of 16 subjects were withdrawn from the study due to adverse events: 7 from the celecoxib group, 7 from the naproxen group, and 2 from the placebo group. Twelve (12) subjects discontinued the study due to treatment-related AEs: 6, 4 and 2 subjects in the celecoxib, naproxen, and placebo treatment groups, respectively.

UGI events, specifically, moderate or severe nausea, abdominal pain, and/or dyspepsia, were experienced by a total of 10 subjects (6 in the naproxen group, and 4 in the placebo group); no UGI events were reported for the celecoxib treatment group. Statistically significant differences between the treatment groups were observed in favor of celecoxib ( $p=0.029$  for the comparison of naproxen vs celecoxib and  $p=0.013$  for the comparison of celecoxib vs placebo).

Two SAEs, severe accidental nasal bone fracture resulting in temporary discontinuation of study medication, was reported by a subject in the naproxen treatment group and prostate malignancy and prostatectomy was reported post-study by a subject in the celecoxib treatment group. Both subjects had completed the study and neither event was judged to be related to study treatment.

**CONCLUSION:** The results of this study indicate that there were no significant differences among 3 treatment groups (celecoxib 200 mg *QD*, naproxen 500 mg *BID*, and placebo) in the treatment of the signs and symptoms associated with OA of the knee. Celecoxib was proven to be safe and well tolerated in this study population..

**Based on report completed:** 15 Apr 2003