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See Drug Details page of this website for approved drug label.

Proprietary Drug Name	INN	Therapeutic area and FDA approved indications
Celebrex	Celecoxib	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

Name of Sponsor/Company: Pfizer Inc.

Title of Study: Study A3191063
A Study of the Efficacy and Tolerability of Once Daily Celebrex® (celecoxib) and Three Times Daily Ibuprofen vs. Placebo in the Treatment of Subjects with Osteoarthritis of the Knee

Study centre(s): 32 US centers

Publication (reference, if applicable): See attached bibliography.

Studied period: 22 Oct 2002 - 10 Mar 2003

Phase of development: Phase 4

Objectives:

The primary objective of this study was to determine whether celecoxib, 200 mg once daily (*QD)*, was as effective as ibuprofen, 800 mg 3 times daily (*TID*), in the treatment of symptoms associated with osteoarthritis (OA) of the knee.

The secondary objective of this study was to confirm the tolerability of celecoxib, 200 mg *QD*, versus placebo in this population of subjects; a tertiary objective was to determine the use of complementary and alternative medicines in this population at screening.

Methodology:

This was a 6-week, multicenter, randomized, double-blind, placebo-controlled, active-comparator, parallel-group study in 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 *QD*, ibuprofen 800 mg *TID*, or placebo, in a 2:2:1 ratio. The study included 4 clinic visits: Screening, Baseline, Week 2 and Week 6 or early termination. The Screening visit occurred within 1 to 14 days prior to the first dose of study medication. During this period, subjects discontinued NSAID and/or analgesic therapy. Acetaminophen (up to 2 g/day) was permitted as rescue analgesia for the treatment of arthritis symptoms during the Screening period. Subjects were to discontinue use of acetaminophen at least 24 hours prior to the Baseline arthritis assessments. Subjects had a medical and medication history, physical examination, vital signs, and underwent clinical laboratory testing. If female of childbearing potential, subjects received a urine pregnancy test (UPT). In addition, an evaluation of arthritis, consisting of both subject and physician assessments, was performed. Subjects completed a

Patient Health Questionnaire, Pain Satisfaction Scale information, and a Complementary and Alternative Medicines Questionnaire.

Subjects who demonstrated an arthritis flare and were eligible for study enrollment returned for their Baseline visit 1 to 14 days after stopping their NSAID/analgesic. Subjects completed Baseline arthritis assessments and verification of flare criteria. The arthritis assessments included Assessments of Arthritis Pain visual analogue scale (VAS), Global Assessments of Arthritis by subject and physician, Functional Capacity Classification criteria, and Western Ontario and McMaster Universities (WOMAC) index questionnaires. Subjects were stratified into 2 groups, based on a Baseline assessment of VAS $\leq$ 69 mm or $\geq$ 70 mm, and randomized to treatment. Concomitant medication, vital signs and AE information was recorded, and the American Pain Society (APS) Pain Measure diary was dispensed. The APS Pain Measure diary was to be completed daily for the first 7 days of the study by the subject starting at Baseline. Use of analgesic medication other than the study medication for treatment of arthritis symptoms was prohibited throughout the study period.

The Week 2 visit occurred 14 $\pm$ 2 days after the first dose of study medication was taken. Concomitant medication, vital signs and AE information was recorded, and study medication and the APS Pain Measure diary were collected. New medication was dispensed and Week 2 arthritis assessments (VAS and an evaluation of arthritis, consisting of both subject and physician assessments) were completed. The Week 6 visit occurred 42 $\pm$ 4 days after the first dose of study medication was taken. Concomitant medication and AE information was recorded, and study medication was collected. Subjects had a physical examination with vital signs, and underwent clinical laboratory testing. In addition, each subject completed the Week 6 arthritis assessments (VAS, evaluation of arthritis, consisting of both subject and physician assessments, and WOMAC), Pain Satisfaction Scale and Patient Health Questionnaire. Subjects who discontinued early from the study completed all Week 6 visit procedures.

Number of patients (planned and analyzed):

Approximately 300 subjects were planned to be enrolled at 20 study centers and randomized in a 2:2:1 manner to celecoxib (120 subjects), ibuprofen (120 subjects), and placebo (60 subjects), respectively. Actual enrollment was 393 randomized subjects (165, 155 and 73 subjects in the celecoxib, ibuprofen, and placebo treatment groups, respectively) at 32 centers. A total of 386 subjects were included in the safety population, 380 subjects were included in the modified intent-to-treat (MITT) population, and 282 subjects were included in the efficacy evaluable population.

Diagnosis and main criteria for inclusion:

Healthy subjects at least 40 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) or analgesic therapy were required to discontinue medications at least 48 hours prior to the Baseline assessments. Subjects indicated an Assessment of Arthritis Pain VAS score between 40 and 90 mm and showed an increase of 1 or more grades in the Physician's and Patient's Global Assessments of Arthritis at the Baseline visit. Subjects who were not receiving any treatment for their OA and whose OA was not controlled were required to have an Assessment of Arthritis Pain VAS score between 40 and 90 mm and a rating of poor or very poor 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 1 celecoxib 200 mg capsule and 1 placebo tablet identical to ibuprofen daily with the morning meal, 1 placebo tablet identical to ibuprofen with midday meal, and 1 placebo tablet identical to ibuprofen daily with the evening meal.

Reference therapy, dose and mode of administration:

Ibuprofen treatment: Subjects randomized to the ibuprofen treatment group were treated with ibuprofen 800 mg *TID* for 6 weeks. They were instructed to take 1 capsule and 1 tablet (1 placebo capsule identical to celecoxib and one 800 mg ibuprofen tablet) with the morning meal, one 800 mg ibuprofen tablet with the midday meal, and one 800 mg ibuprofen tablet with the evening meal.

Subjects randomized to the placebo treatment group were treated with placebo for 6 weeks. They were instructed to take 1 placebo capsule (identical to celecoxib and 1 placebo tablet identical to ibuprofen) with the morning meal, 1 placebo tablet identical to ibuprofen with the midday meal, and 1 placebo tablet identical to ibuprofen with the evening meal. The placebos were similar in size, color, smell, taste and appearance to the study medication.

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 WOMAC Osteoarthritis Index from Baseline to Week 6/Early Termination, change in APS pain scores from Baseline to first 7 days post treatment, the Pain Satisfaction Scale, the Patient Health Questionnaire (PHQ-9), and measurement of Upper Gastrointestinal (UGI) Tolerability. The Complementary and Alternative Medicines Questionnaire Worksheet was completed at the Screening visit.

Safety:

General clinical safety was assessed by the monitoring of treatment-emergent adverse events (AEs), vital signs, and the results of physical examination.

Statistical methods:

The primary analysis population was the Per Protocol Analysis (PPA) population (or Efficacy Evaluable 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, and taken study medication within 48 hours prior to Week 6 visit.

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 ibuprofen if the lower bound of the 2-sided 95% confidence interval of the treatment difference (ibuprofen – celecoxib) lay above -10 mm in the PPA population. As a test of internal control, the primary efficacy parameter was also tested for the differences between celecoxib vs placebo and ibuprofen 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 using MITT population to avoid biased results caused by informative dropouts among treatment groups. 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 scores 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. Pain Satisfaction Scale was analyzed using CMH test stratified by center.

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 in PPA population. This was the only primary efficacy analysis performed in the study; that provided the comparison between celecoxib and ibuprofen using non-inferiority criteria on the PPA population.

	Celecoxib	**Ibuprofen**	**Placebo**
Baseline			
N	119	118	45
Mean	68.2	65.7	66.0
SE Mean	1.0	1.3	1.9
Week 6			
N	119	118	45
Mean	28.2	26.4	33.4
SE Mean	2.0	2.1	3.6
Change from Baseline			
N	119	118	45
Mean	-40.0	-39.4	-32.5
SE Mean	2.0	2.4	3.7
	Ibuprofen-Celecoxib	**Ibuprofen-Placebo**	**Celecoxib-Placebo**
LS Mean	-0.77	-7.64	-6.87
SE	2.96	3.92	3.96
95% CI	[-6.6, 5.1]	[-15.4, 0.1]	[-14.7, 0.9]
p-value	0.7944	0.0528	0.0842

The celecoxib treatment was observed to be as effective as ibuprofen since the lower bound of the 2-sided 95% CI on the difference (ibuprofen-celecoxib) was –6.6 mm, which is greater than the protocol-defined non-inferiority margin of –10 mm. Similar results were obtained at Week6 using MITT population.

Both active treatments showed a statistically significant difference compared to placebo group in the MITT population (p-value = 0.018 for ibuprofen vs. placebo and p-value = 0.014 for celecoxib vs. placebo). These significant results were further confirmed by the change of WOMAC pain domain score from baseline at Week 6 (p-value = 0.03 for ibuprofen vs. placebo, and p-value = 0.04 for celecoxib vs. placebo).

Secondary Efficacy: Secondary efficacy analyses were performed on the MITT population with the exception of the analysis of UGI events, which was performed on the safety population. The results for the secondary efficacy endpoints were similar between active treatments for the Patient's Global Assessment of Arthritis, the WOMAC OA Index scores, the Pain Satisfaction Scale and the Patient Health Questionnaire. Statistically significant treatment effects were seen in the Week 6 Patient's assessment of arthritis pain (VAS) (p = 0.0323) and approached significance for Week 6 Physician's Global Assessment (p = 0.0504). Statistical significance were shown in the change of WOMAC pain domain score from baseline at Week 6 (p-value = 0.03 for ibuprofen vs. placebo, and p-value = 0.04 for celecoxib vs. placebo) and in the Physician's Global Assessment of arthritis at Week 6 (p-value = 0.0149 for celecoxib vs. placebo). Mean changes from Screening in the individual components of question 1B were statistically significant in favor of celecoxib over placebo with respect to changes in depression (p=0.0235) and question 1H for moving slowly or becoming restless (p = 0.0451), in favor of celecoxib over ibuprofen with respect to changes in depression, question 1B (p=0.0296) and in favor of ibuprofen over placebo with respect to question 1E, changes in appetite (p = 0.0423). There was a trend for the superiority of both active treatments over placebo across almost all efficacy measures. Also, both treatments were similar and of comparable efficacy in all efficacy measures.

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 primarily GI system disorders, psychiatric disorders, central and peripheral nervous disorders, and general and respiratory disorders. Among the AEs, only depression, nausea and headache occurred in > 5% of the subject population. A total of 21 subjects were withdrawn from the study due to adverse events: 6 from the celecoxib group, 10 from the ibuprofen group, and 5 from the placebo group. Fifteen (15) subjects discontinued the study due to treatment-related AEs: 3, 8 and 4 subjects in the celecoxib, ibuprofen, and placebo treatment groups, respectively. UGI events, specifically, moderate or severe nausea, abdominal pain, and/or dyspepsia were experienced by a total of 14 subjects (3 in the celecoxib group, 9 in the ibuprofen group, and 2 in the placebo group). The difference between celecoxib and ibuprofen approached statistical significance in the incidence of UGI events ($p = 0.0811$). A subject in the celecoxib treatment group reported one SAE, severe pelvic inflammation, which resulted in discontinuation of subject from the study. The event was not related to study treatment and resolved completely.

CONCLUSION:

The results of this study indicate that celecoxib 200 mg *QD* was not inferior to ibuprofen 800 mg *TID* 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 prepared on: 23 March 2004