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Prescribing decisions should be made based on the approved package insert

Link to 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 A3191053

A Study of the Efficacy and Tolerability of Once Daily Celebrex® (celecoxib) and Twice Daily Naproxen vs Placebo in the Treatment of Hispanic Subjects with Osteoarthritis of the Knee

Study centre(s): Thirty-one (31) investigators enrolled subjects at 31 study centers in the USA.

Publication: None

Studied period 05 Nov 2001 – 20 Nov 2002 **Phase of development:** Phase 4

Objectives: The primary objective of this study was to determine whether celecoxib, 200 mg taken once daily *(Q*D), was as effective as naproxen, 500 mg taken twice daily *(BI*D), in the treatment of symptoms associated with osteoarthritis (OA) of the knee. The secondary objective was to confirm the tolerability of celecoxib, 200 mg *Q*D, versus placebo in Hispanic subjects; the 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 Hispanic 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 *Q*D, naproxen 500 mg *BI*D, or placebo, in a 2:2:1 ratio. 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] ≤69 mm or ≥70 mm and randomized to receive treatment. Use of analgesic medication (other than the study medication) for arthritis symptoms was prohibited throughout the study period. Subjects returned for the Week 2 visit, for the Week 2 arthritis assessments and to receive additional study medication. In addition, concomitant medication and adverse event (AE) information was recorded. At the Week 6 visit each subject completed the Week 6 arthritis assessments, the Pain Satisfaction Scale and 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 318 randomized subjects (127, 129, and 62 subjects in the celecoxib, naproxen, and placebo treatment groups, respectively). A total of 315 subjects received treatment. All treated subjects were included in the safety and modified intent-to-treat (MITT) populations; 239 subjects were included in the PPA population.

Diagnosis and main criteria for inclusion: Healthy Hispanic subjects at least 45 years old, with diagnosed OA 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 to have 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 examinations.

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") and a general linear model with treatment and center effects in the model 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 celecoxib treatment was observed to be as effective as naproxen according to protocol requirements, since the lower bound of the 2-sided 95% CI of the treatment difference (naproxen-celecoxib) was above –10mm (-3.8mm). The p-values for celecoxib vs. placebo (p=0.0077) and naproxen vs. placebo (p=0.0407) suggest that, in this study, both celecoxib and naproxen were significantly more effective than placebo at relieving pain, as recorded on the Patient's Assessment of Arthritis Pain VAS.

Secondary Efficacy: The results for the secondary efficacy endpoints were similar between active treatments. The Patient's and Physician's Global Assessment of Arthritis, the WOMAC OA Index scores, UGI tolerability, the Pain Satisfaction Scale and the Patient Health Questionnaire showed no statistically significant differences between celecoxib and naproxen treatment groups.

SAFETY RESULTS The incidence of AEs and treatment-related AEs were 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 occurred in >5% of the subject population. A total of 13 subjects were withdrawn from the study due to adverse events: 3 from the celecoxib group, 9 from the naproxen group, and 1 from the placebo group. Ten (10) subjects discontinued the study due to treatment-related AEs: 2, 7, and 1 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 8 subjects (3 in the celecoxib group, 4 in the naproxen group, and 1 in the placebo group). No statistically significant differences in UGI tolerability were observed among the treatment groups. One SAE, GI hemorrhage, which was considered related to study treatment and resulted in discontinuation of study medication, was reported by a subject in the naproxen treatment group.

The results of this study indicate that there was no difference between celecoxib 200 mg *QD* and naproxen 500 mg *BID* in the treatment of the signs and symptoms associated with OA of the knee, as defined by this protocol. Celecoxib was proven to be safe and well tolerated in this study population.

Based on report prepared on: 26 March 2003