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PROPRIETARY DRUG NAME/INN: Celebrex®/Celecoxib

THERAPEUTIC AREA AND FDA APPROVED INDICATIONS:

- For relief of the signs and symptoms of osteoarthritis.
- For relief of the signs and symptoms of rheumatoid arthritis in adults.
- For the management of acute pain in adults.
- For the treatment of primary dysmenorrhea.
- To reduce the number of adenomatous colorectal polyps in familial adenomatous polyposis (FAP), as an adjunct to usual care (e.g., endoscopic surveillance, surgery).

PROTOCOL NO. 635-IFL-0508-003

PROTOCOL TITLE: A Double-Blind, Placebo-Controlled, Randomized Six Week Comparison Study of the Efficacy of Celecoxib 200 mg QD and Rofecoxib 25 mg QD in Relieving the Signs and Symptoms of Osteoarthritis of the Knee

Study Center(s): Sixty-one (61) study centers, including 51 in the United States and 10 in Canada.

Study Initiation and Completion Dates: 16 April 2001 to 19 July 2001

Phase of Development: Phase 4

Study Objective(s):

Primary objective:

To compare the efficacy of celecoxib, rofecoxib, and placebo in relieving the signs and symptoms of a flare of osteoarthritis (OA) of the knee.

Secondary objective:

To compare the overall safety of celecoxib 200 mg once daily (QD) and rofecoxib 25 mg QD to placebo.

METHODS

Study Design: This was a double-blind, placebo-controlled, randomized, multicenter, parallel-group study comparing the efficacy of celecoxib, rofecoxib, and placebo in relieving the signs and symptoms of a flare of OA of the knee. Patients who met the flare criteria were randomly assigned to receive either celecoxib 200 mg QD, rofecoxib 25 mg QD, or placebo. The study had a pretreatment Screening period of up to 14 days followed by a 6-week treatment period. Patients who were receiving a nonsteroidal antiinflammatory (NSAID) and/or analgesic drug to control

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their arthritis symptoms at Screening had to discontinue their current arthritis medication and complete a washout period of two days minimum prior to Baseline Assessments and randomization. Visits occurred at Screening and Baseline (Day 0) and at Week 3 and Week 6/Early Termination during the treatment period.

470 patients were planned (celecoxib 200 mg QD, 188 patients; rofecoxib 25 mg QD, 188 patients; placebo, 94 patients) and 477 patients were enrolled (celecoxib 200 mg QD, 189 patients; rofecoxib 25 mg QD, 190 patients; placebo, 98 patients). Two patients in the placebo group were randomized but did not receive study drug. Data for all patients who received at least one dose of study medication (n = 475) were evaluated for safety and efficacy in the Intent-to-Treat analysis.

Diagnosis and Main Criteria for Inclusion: To qualify for study enrollment, each patient had to satisfy the following main eligibility criteria:

- Classification of American College of Rheumatology (ACR) criteria as having OA of the knee;
- Functional Capacity Classification of I-III at the Screening Visit;
- OA in a flare state at the Baseline Visit;
- Age 40 years of age or older; and
- If female and of childbearing potential, the patient had to be using adequate contraception since her last menses, had to use adequate contraception during the study, could not be lactating, and had to have a negative serum or urine pregnancy test within 14 days before the Baseline Arthritis Assessments.

Study Treatment:

- Celecoxib 200 mg capsules
- Placebo matching celecoxib 200 mg capsules
- Rofecoxib 25 mg capsules (encapsulated for blinding purposes)
- Placebo matching rofecoxib 25 mg capsules

Patients in the celecoxib treatment arm were instructed to take one capsule of celecoxib and one placebo capsule matching the rofecoxib capsule, once daily with the evening meal.

Patients in the rofecoxib treatment arm were instructed to take one capsule each of rofecoxib and placebo matching the celecoxib capsule, once daily with the evening meal.

Patients in the placebo treatment arm were instructed to take one placebo capsule matching the celecoxib capsule and one placebo capsule matching the rofecoxib capsule, once daily with the evening meal.

The total duration of treatment was six (6) weeks.

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Efficacy Evaluations:

Primary efficacy variables:

- Patient's Assessment of Arthritis Pain - Visual Analog Scale (OA Pain-VAS); and
- Western Ontario and McMaster Universities (WOMAC) Total Scores.

Secondary efficacy variables:

- Patient's Global Assessment of OA;
- WOMAC Pain Domain, Stiffness Domain, and Physical Function Scores;
- Patient's Assessment of Arthritis Pain - Visual Analog Scale (Pain on Walking-VAS);
- OA Severity Index (OASI);
- Physician's Global Assessment of Arthritis;
- Patient's Satisfaction Assessments; and
- Patient's Willingness to Continue Study Medication.

Pharmacokinetic, Pharmacodynamic, and/or Other Evaluations: No pharmacokinetic or pharmacodynamic evaluations were performed.

Safety Evaluations: Safety assessments included:

- Adverse Events;
- Clinical Laboratory Values; and
- Vital Signs and Weight.

Statistical Methods: Analyses for normally-distributed efficacy parameters at each visit (as specified above) were performed using a generalized linear mixed model with pooled investigator center as a random effect, and Baseline score and Baseline Assessment of Arthritis Pain stratification as fixed effects. Three tests for treatment effects were performed: celecoxib 200 mg QD vs rofecoxib 25 mg QD, celecoxib 200 mg QD vs placebo, and rofecoxib 25 mg QD vs placebo. The difference in the least squares (LS) mean, the standard error of the differences, the 95% confidence interval of the difference, and the p-values were presented for each test.

Patient's Global Assessment of Arthritis and Physician's Global Assessment of Arthritis were analyzed at each visit using the proportional odds logistic regression method with adjustment for Baseline score and Baseline Assessment of Arthritis Pain stratification. Changes from Baseline in Patient's and Physician's Global Assessment of Arthritis were analyzed similarly. Three tests for treatment effects were performed: celecoxib 200 mg QD vs placebo, rofecoxib 25 mg QD vs placebo, and celecoxib 200 mg QD vs rofecoxib 25 mg QD. The effect size, the standard error for effect size, the odds ratio, the 95% confidence interval for the odds ratio, and the p-value were presented for each test. Significance for all tests was evaluated relative to $\alpha = 0.05$. No adjustments for multiple comparisons were made.

Treatment-emergent adverse events were displayed descriptively by incidence overall and with respect to severity, attribution, events leading to withdrawal, and serious adverse events according to the World Health Organization Adverse Reaction Terminology (WHOART) by body system and preferred term. Laboratory parameters and vital signs data were analyzed as the change from Screening to Week 6/Final Visit with respect to each treatment groups using one-

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way analysis of variance F-tests. Summary statistics were displayed for vital sign data, and paired t-tests were used to analyze the change from Baseline to Week 6/Final Visit within treatment groups.

RESULTS

Subject Disposition and Demography: Of the 477 patients enrolled in the study, two patients in the placebo treatment group did not receive drug. Of the 475 patients treated, 383 completed the study (158 in the celecoxib 200 mg QD group; 161 in the rofecoxib 25 mg QD group; 64 in the placebo group). Reasons for withdrawal were similar across treatment groups, with the exception of withdrawal due to treatment failure. A higher percentage of patients in the placebo group (21/98 [21%]) withdrew due to treatment failure than in the celecoxib 200 mg QD (10/189 [5%]) and rofecoxib 25 mg QD groups (10/190 [5%]). Two (2) patients in the celecoxib 200 mg QD group and 3 each in the rofecoxib 25 mg QD and placebo groups withdrew for “other” reasons (including patients who moved away, went on vacation, had study medications stolen, or withdrew consent for personal reasons). One (1) patient in the placebo group died.

The ITT population included 475 patients (189 patients in the celecoxib 200 mg QD group; 190 patients in the rofecoxib 25 mg QD group ; 96 patients in the placebo group) who received study treatment. Analyses based on the Evaluable for Efficacy cohort included data from 178 patients in the celecoxib 200 mg QD group, 181 patients in the rofecoxib 25 mg QD group, and 91 patients in the placebo group.

There were no statistically significant differences across treatment groups with respect to age, gender, race, height, weight, and vital signs.

The mean duration of OA was comparable across the treatment groups, and the medical history of patients in the three treatment groups was comparable with respect to cardiovascular history, urogenital history, GI history, use of prescreening NSAIDs and/or analgesics for OA, and ASA used for cardiac prophylaxis. There were no statistically significant differences across treatment groups in the arthritis measurements employed in the study.

Efficacy Results: The results of this study establish the non-inferiority of celecoxib 200 mg QD as compared to rofecoxib 25 mg QD in treating the signs and symptoms of OA flare of the knee. Based on LS means of changes from Baseline among patients in the Evaluable for Efficacy cohort, the results of non-inferiority tests for the primary efficacy measures (Patient’s Assessment of Arthritis Pain and the Total Domain scores for WOMAC Osteoarthritis Index at Week 6/Early Termination) demonstrate the clinical equivalence of celecoxib and rofecoxib. For Patient Assessment of Arthritis Pain at Week 6/Early Termination, the results of tests for noninferiority demonstrate the clinical equivalence of celecoxib and rofecoxib, based on an upper 95% confidence limit of 1.9, a value well within the restriction (the upper confidence limit for the difference in LS means cannot exceed 10, the predefined, clinically relevant cutoff point) to reject the null hypothesis of inferiority. Likewise, for the Total Domain Score for WOMAC Osteoarthritis Index at Week 6/Early Termination, the results of tests for non-inferiority demonstrate the clinical equivalence of celecoxib and rofecoxib, based on an upper 95% confidence limit of 1.0, a value well within the restriction (the upper confidence limit for the difference in LS means cannot exceed 5.5, the predefined, clinically relevant cutoff point) to

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reject the null hypothesis of inferiority. The conclusion that celecoxib 200 mg QD is comparable to rofecoxib 25 mg QD in treating the signs and symptoms of OA flare of the knee is supported by results of the primary analyses for patients in the ITT cohort.

The results of this study also support the conclusion that both celecoxib 200 mg QD and rofecoxib 25 mg QD are significantly more effective than placebo for relieving the signs and symptoms of OA flare of the knee. This was evidenced by the fact that, when comparing the primary efficacy measures at Week 6/Early Termination, the differences between the active treatment groups and placebo were statistically significant. Accordingly, greater improvement in Patient's Assessment of Osteoarthritis Pain – VAS at Week 6/Early Termination was observed when each active treatment was compared with placebo, as shown by the significant differences in LS means of change from Baseline for celecoxib 200 mg QD ($p < 0.001$) and rofecoxib 25 mg QD ($p = 0.001$) compared with placebo. Likewise greater improvement was observed in the WOMAC Total Domain scores at Week 6/Early Termination with celecoxib 200 mg QD and rofecoxib 25 mg QD compared with placebo, as shown by the significant differences in the LS means of change from Baseline between the celecoxib 200 mg QD group and the placebo group and between the rofecoxib 25 mg QD group and the placebo group (both $p < 0.001$).

Similar findings were observed for the secondary efficacy measures, all of which were analyzed using data from patients in the ITT cohort. Statistically significant improvement was observed at all analyzed timepoints relative to placebo for both celecoxib 200 mg QD and rofecoxib 25 mg QD in the absolute scores and change values in Patient's Global Assessment of Osteoarthritis; Patient's Assessment of Osteoarthritis Pain – VAS; the pain, stiffness, and physical functioning components of the WOMAC Osteoarthritis Index; Patient's Assessment of Pain on Walking – VAS; absolute and change values in Physician's Global Assessment of Arthritis; OASI; Patient's Satisfaction Assessment of Pain Relief and Walking and Bending Ability; and Patient's Willingness to Continue Study Medication. There were no statistically significant differences between celecoxib 200 mg QD and rofecoxib 25 mg QD with regard to any of the secondary assessments, indicating the comparability of these treatments in relieving the signs and symptoms of OA flare of the knee.

Pharmacokinetic, Pharmacodynamic, and/or Other Results: No pharmacokinetic or pharmacodynamic evaluations were performed.

Safety Results: Celecoxib 200 mg QD was safe and well-tolerated for the 6-week duration of this study in patients with OA of the knee. Overall, the nature and frequency of treatment-emergent adverse events were similar between the celecoxib 200 mg QD and rofecoxib 25 mg QD groups. Higher incidences of treatment-emergent adverse events were reported by patients in the celecoxib 200 mg QD group and the rofecoxib 25 mg QD group compared with the placebo group. Most adverse events were mild or moderate in severity and considered by the Investigator to be unrelated to study medication.

Twenty-six (26) patients withdrew from the study due to adverse events: 11 (6%) patients in the celecoxib 200 mg QD group, 10 (5%) patients in the rofecoxib 25 mg QD group, and 5 (5%) patients in the placebo group. Treatment-emergent adverse events of the GI system, the body as a whole, and the central and peripheral nervous system were the most frequent causes of withdrawal from the study.

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Across the three treatment groups, a total of seven patients had serious adverse events. A total of three serious adverse events (angioedema, bronchospasm, and neoplasm) were reported for 3 patients in the celecoxib 200 mg QD group (1.6%), one serious adverse event (endometrial neoplasm malignant) was reported for one patient in the rofecoxib 25 mg QD group (0.5%), and four serious adverse events (carcinoma, death 'not otherwise specified,' GI hemorrhage, and unstable angina) were reported for 3 patients in the placebo group (3.1%). Only one serious adverse event, angioedema (in the celecoxib 200 mg QD group), was considered by the investigator to be related to study medication.

There was one death during this study. One patient in the placebo group died due to a serious adverse event reported as: death 'not otherwise specified.' The patient was a 74-year-old male with a history of diabetes, coronary disease, hypertension, and hyperlipidemia. On Day 22 of the study, he died suddenly due to cardiorespiratory arrest secondary to coronary artery disease and hypertension. The investigator considered that the event was not related to study drug.

Within each subgroup of patients who either did or did not use acetylsalicylic acid (ASA) as a cardiac prophylactic, the percentages of patients who had moderate or severe upper gastrointestinal (UGI) discomfort (abdominal pain, dyspepsia, or nausea) were not significantly different among the treatment groups.

For changes in ALT (SGPT) and AST (SGOT), differences among the treatment groups were not statistically significant. Differences among the treatment groups in BUN were significant ($p < 0.001$); all mean changes were increases from Screening, with the smallest increase observed in the placebo group (0.029 mmol/L) and the largest observed in the rofecoxib 25 mg QD group (0.788 mmol/L). For creatinine, the changes observed in the celecoxib 200 mg QD group and the placebo group were decreases from Screening (-0.726 $\mu\text{mol/L}$ and -1.046 $\mu\text{mol/L}$, respectively), whereas an increase was observed among patients in the rofecoxib 25 mg QD group (3.114 $\mu\text{mol/L}$); these differences were significant ($p = 0.003$). For hematocrit, the changes observed in the three treatment groups were slight decreases; although the decrease observed among patients in the rofecoxib 25 mg QD group (-0.008) was statistically greater ($p = 0.005$) than those observed among patients in the celecoxib 200 mg QD group (-0.001) and the placebo group (0.000). For hemoglobin, the changes observed in the celecoxib 200 mg QD group (0.436 g/L) and the placebo group (0.628 g/L) were increases from Screening, whereas a decrease was observed among patients in the rofecoxib 25 mg QD group (-1.516 g/L); these differences were also significant ($p = 0.013$).

The mean values for ALT (SGPT), AST (SGOT), BUN, creatinine, hematocrit, and hemoglobin for all treatment groups were within normal ranges at Screening and remained within normal ranges at the Week 6/Early Termination Visit. No patient withdrew from the study due to a clinically relevant laboratory value. There were no clinically important differences across treatment groups with respect to clinically relevant changes in weight, pulse, or blood pressures.

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Incidence of Treatment - Emergent Adverse Events in $\geq 2\%$ of Patients in Any Treatment Group			
Adverse Event	Celecoxib 200 mg QD (N=189)	Rofecoxib 25 mg QD (N=190)	Placebo (N=96)
Headache	15 (7.9%)	9 (4.7%)	4 (4.2%)
Dyspepsia	11 (5.8%)	10 (5.3%)	3 (3.1%)
Diarrhea	8 (4.2%)	5 (2.6%)	1 (1.0%)
Edema Peripheral	5 (2.6%)	8 (4.2%)	2 (2.1%)
Rhinitis	5 (2.6%)	2 (1.1%)	1 (1.0%)
Abdominal Pain	3 (1.6%)	2 (1.1%)	2 (2.1%)
Sinusitis	3 (1.6%)	6 (3.2%)	0 (0%)
Injury-Accidental	2 (1.1%)	4 (2.1%)	2 (2.1%)
Upper Respiratory Tract Infection	2 (1.1%)	1 (0.5%)	2 (2.1%)
Dizziness	1 (0.5%)	5 (2.6%)	1 (1.0%)
Hypertension	1 (0.5%)	6 (3.2%)	0 (0%)
Cramps Legs	0 (0%)	4 (2.1%)	0 (0%)

Adverse Events are sorted by descending total incidence in the celecoxib 200 mg QD group.

Conclusion(s): Celecoxib 200 mg QD and rofecoxib 25 mg QD were clinically equivalent in treating the signs and symptoms of OA flare of the knee, as shown by results of statistical tests of non-inferiority. Furthermore, both active treatments were comparably and significantly superior to placebo with respect to both primary and secondary efficacy measures. No unexpected treatment-emergent adverse events were noted for patients treated with celecoxib 200 mg QD or rofecoxib 25 mg QD in this study. No new safety concerns were raised by the data in this study.

Based on a report completed on: 6 November 2001.