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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 as an adjunct to usual care.

PROTOCOL NO. N49-96-02-013

PROTOCOL TITLE: Revised Integrated Clinical and Statistical Report for a Pilot Dose-Ranging Study to Evaluate the Safety and Efficacy of SC-58635 (Celecoxib) 40 mg, 100 mg, and 200 mg BID Versus Placebo in Treating the Signs and Symptoms of Osteoarthritis

Study Center(s): Twenty-four (24) study centers in the United States.

Study Initiation and Completion Dates: 26 January 1996 to 15 April 1996

Phase of Development: Phase 2

Study Objective(s):

1. Evaluate the effectiveness of SC-58635 at doses of 40 mg BID, 100 mg BID, and 200 mg BID versus placebo in treating the signs and symptoms of OA;
2. Determine the effective dose range of SC-58635 in the treatment of the signs and symptoms of OA; and
3. Evaluate the safety of SC-58635 at doses of 40 mg BID, 100 mg BID, and 200 mg BID for two weeks in patients with OA.

METHODS

Study Design: This was a double-blind, placebo-controlled, multicenter, parallel group comparison of the efficacy of SC-58635 versus placebo in treating the signs and symptoms of OA. The study consisted of a Pretreatment period within 14 days of the start of study medication and a two-week Treatment period. Patients who met the entry criteria were randomly assigned to receive either 40 mg BID, 100 mg BID, or 200 mg BID SC-58635 or placebo BID for two weeks.

A target sample size of 240 (60 patients per treatment arm) was selected for this study in order to allow detection of a statistically significant difference in change from Baseline between an active treatment group and the placebo group with 80% power and at an alpha level of 0.05. Two

hundred ninety-three (293) patients were enrolled at 24 sites in this study and were randomized to receive one of four treatments: 71 patients received placebo, 73 patients received SC-58635 40 mg BID, 76 patients received SC-58635 100 mg BID, and 73 patients received SC-58635 200 mg BID.

Diagnosis and Main Criteria for Inclusion: Male and female subjects 18 years of age or older were eligible if they had osteoarthritis of the knee in a flare state, a Functional Capacity Classification of I-III, and had not received any nonsteroidal anti-inflammatory drugs or analgesics in the two days prior to receiving the first dose of study medication.

Study Treatment: Investigational drug supplies consisted of the following: capsules containing 20 mg SC-58635; capsules containing either 100 mg or 200 mg SC-58635, each identical in size and color; placebo capsules identical in size and appearance to the 20 mg SC-58635 capsules; and placebo capsules identical in size and appearance to the 100 mg and 200 mg SC-58635 capsules. Study treatment consisted of three capsules administered twice daily for two weeks.

Efficacy Evaluations:
Primary measures of arthritis efficacy:

- Physician's Global Assessment of Arthritic Condition
- Patient's Global Assessment of Arthritic Condition
- Osteoarthritis Severity Index

Secondary measures of arthritis efficacy:

- Functional Capacity Classification
- Patient Assessment of Arthritis Pain-Visual Analog Scale (VAS)
- SF-36 Health Survey
- Incidence of Withdrawal Due to Lack of Arthritis Efficacy
- Time to Withdrawal

Pharmacokinetic, Pharmacodynamic, and/or Other Evaluations: One 15 mL blood sample for pharmacokinetic testing was obtained during the Week 1 Visit, but was analyzed for plasma concentration of study drug only.

Safety Evaluations: Safety was measured by the record of treatment-emergent adverse events, clinical laboratory tests, changes from Baseline in vital signs and temperature, and physical examinations.

Statistical Methods: Summary statistics for all randomized patients were tabulated by treatment group. The Kruskal-Wallis test was performed to determine whether the randomization was successful in creating treatment groups that exhibited only chance variations at Baseline with respect to age, height, weight, and vital signs. Homogeneity of treatment groups in terms of gender and race was analyzed by the Fisher's exact test. Differences between the treatment groups with respect to history of GI bleeding, gastroduodenal ulcer, cardiovascular disease, GI NSAID intolerance (defined as nausea, dyspepsia and/or diarrhea without evidence of ulcer), and OA Index Knee were also analyzed with Fisher's exact test. Baseline differences in duration of OA were analyzed with the Kruskal-Wallis test.

Baseline results of Physician's Global Assessment of Arthritic Condition, Patient's Global Assessment of Arthritic Condition, and Functional Capacity Classification were analyzed for differences among treatment groups with the Cochran-Mantel-Haenszel (CMH) test stratified by center. The Osteoarthritis Severity Index and Patient's Assessment of Arthritis Pain were analyzed with a Kruskal-Wallis test. Baseline SF-36 Health Survey scores were analyzed with an analysis of covariance (ANCOVA) with treatment group and center as factors.

The primary analyses for the primary measures of efficacy consisted of the following: Analyses of mean change at each post-Baseline Visit performed by analysis of covariance (ANCOVA) with treatment and center as factors and the corresponding Baseline Arthritis Assessment score as the covariate; a linear trend test to investigate dose response; and an overall and pairwise comparison for all four treatment groups. The linear trend tests and pairwise comparisons were carried out using contrasts based on the above ANCOVA model. Effects of treatment by Baseline interaction, treatment by center interaction, age, and gender were investigated. If significant effects were observed consistently for Week 1 and Week 2, then subgroup analyses based on the effect were performed, if appropriate. The analyses of mean change and the linear trend test analyses were performed using SAS general linear models procedures with contrast statements for the pairwise treatment group comparisons for the following efficacy variables: Physician's and Patient's Global Assessments and Osteoarthritis Severity Index.

The categorical analyses of change from Baseline for the Physician's and Patient's Global Assessments were not included in the original analysis plan in the protocol but were performed to provide a better understanding of the effectiveness of the study drug. CMH analyses stratified by center were used for linear dose trend tests and treatment group comparisons. Changes from Baseline at each post-Baseline Visit were analyzed also with nonparametric CMH analyses, stratified by center. Linear trend tests and pairwise comparisons based on the above CMH analyses for all treatment groups were also performed.

Baseline SF-36 Health Survey scores were analyzed with an analysis of variance (ANOVA) with treatment group and center as factors. The analyses of the mean changes on the SF-36 Health Survey scores were conducted only for the ITT Cohort. Effects of treatment by Baseline interaction, treatment by center interaction, age, and gender were not examined.

Every randomized patient who received at least one dose of study medication was included in the safety analysis. All adverse events were coded and summarized by treatment group. The incidence of treatment-emergent adverse events was tabulated by treatment group and body system. Clinical laboratory data were summarized and treatment groups compared using the Kruskal-Wallis test applied to change from Baseline to Week 2. Values outside the normal range were identified. Scatter plots were used to graphically depict the results. Shift tables (below, within, and above the normal range) and the Stuart-Maxwell test or McNemar's test, depending on the number of non-zero cells, were used to determine significant distribution changes within treatment groups over the course of the study.

For purposes of statistical analyses of the efficacy variables, a derived SAS efficacy dataset containing demographic characteristics and all the primary and secondary measures of efficacy was created with a one patient/one record structure. All statistical testing was two-sided at the 5% level. All the analyses in this study were performed using SAS version 6.09.

RESULTS

Subject Disposition and Demography: Of the 293 patients in the ITT Cohort, 252 (86%) completed the study. Forty-one patients withdrew without completing the study. A higher proportion of placebo patients (10 [14%]) withdrew because of treatment failure than SC-58635 patients (10 patients in all dose groups [4.5%]). None of the 40 mg patients, five (7%) 100 mg patients, and one (1%) 200 mg patient withdrew from the study as a result of adverse events, compared to two (3%) placebo patients. Overall, a higher percentage of placebo patients (23%) withdrew from the study compared to SC-58635 patients (8% to 13%) in all dose groups.

The treatment groups were comparable for age (range 29 to 92), gender (25% to 37% of all patients were male), height, weight, and vital signs at Baseline, and 84% to 96% of all groups were Caucasian. The small number of Blacks enrolled in the study were unevenly distributed among the treatment groups.

All treatment groups were comparable with respect to history of GI bleeding, gastroduodenal ulcer, cardiovascular disease, and NSAID GI intolerance. All treatment groups were comparable with respect to OA duration and designation of left or right as Index Knee.

The Baseline means for the Patient's Assessment of Arthritis Pain on the VAS, the Physician's Global Assessment of the Arthritic Condition, and the Patient's Global Assessment scores was similar for all treatment groups. There was no statistically significant difference in the mean Osteoarthritis Severity Index among the different treatment groups at Baseline. Mean scores at Baseline for each domain of the SF-36 Health Survey scores were similar across all treatment groups.

Efficacy Results: In both the Physician's Global Assessment and the Patient's Global Assessment, SC-58635 produced a reduction in the signs and symptoms associated with OA compared to placebo. This improvement was statistically significant at Week 1. At Week 2, both the 40 mg and the 200 mg dose groups continued to provide statistically significant relief as determined by the Patient's Global Assessment. The Physician's Global Assessment also determined that at Week 2, the 200 mg dose provided significant improvement in the patient's condition.

Similar results were observed with the Osteoarthritis Severity Index. The SC-58635-treated groups showed greater improvements at both Week 1 and Week 2 than patients in the placebo-treated group. These improvements were significant at Week 1 for the 40 mg and 200 mg dose groups.

Further support for the efficacy of SC-58635 in the treatment of OA was shown by the Patient's Assessment of Arthritis Pain, the Functional Capacity Classification, the SF-36 Health Survey, and withdrawals due to lack of arthritis efficacy. The Patient's Assessment of Arthritis Pain indicated statistically significant improvement at Week 1 for all three active doses and Week 2 for the 100 mg and 200 mg doses. The 200 mg dose produced statistically significant effects compared to placebo in the following domains of the SF-36 Health Survey: Physical Functioning, Role-Physical, Bodily Pain, Vitality, and Social Functioning. Twenty (20) patients withdrew for treatment failure (10 placebo, 6 SC-58635 40 mg, one SC-58635 100 mg, and 3

SC-58635 200 mg); these differences were statistically significant for the 100 mg and 200 mg groups compared with placebo.

Pharmacokinetic, Pharmacodynamic, and/or Other Results: Other than plasma concentration testing at Week 1, no additional pharmacokinetic or pharmacodynamic evaluations were performed.

Safety Results: Adverse events were reported by 30 (43%) of the patients in the placebo group; 30 (41%) of the patients receiving 40 mg SC-58635; 35 (47%) of the patients receiving 100 mg SC-58635; and 36 (49%) of the patients receiving 200 mg SC-58635. Adverse events reported in =5% of patients in any treatment groups are shown below:

ADVERSE EVENTS OCCURRING IN ³5% OF PATIENTS IN ANY TREATMENT GROUP

	Placebo (n= 70)	SC-58635 40mg BID (n= 73)	SC-58635 100mg BID (n= 75)	SC-58635 200mg BID (n= 73)
Headache	12 (17%)	5 (7%)	2 (3%)	11 (15%)
Diarrhea	2 (3%)	5 (7%)	3 (4%)	6 (8%)
Abdominal pain	1 (1%)	2 (3%)	2 (3%)	4 (5%)
Dizziness	0 (0%)	3 (4%)	5 (7%)	3 (4%)
Dyspepsia	7 (10%)	2 (3%)	5 (7%)	3 (4%)
Nausea	0 (0%)	3 (4%)	5 (7%)	2 (3%)
Upper resp tract infection	4 (6%)	3 (4%)	2 (3%)	2 (3%)

Serious adverse events were reported for one patient from the 100 mg SC-58635 group (accidental fracture of the left ankle) and one patient from the 200 mg SC-58635 group (arrhythmia). Neither of these events was determined by the Investigator or the Medical Monitor to be related to the study drug. Eight patients withdrew from study participation as a result of adverse events (two placebo, five 100 mg SC-58635, and one 200 mg SC-58635). There were no deaths during the study. There were no consistent clinically significant alterations in laboratory test values.

Conclusion(s):

- SC-58635 dosages of 40, 100, and 200 mg BID were safe and effective in treating the signs and symptoms of OA.
- SC-58635 40 mg BID was submaximally effective.
- SC-58635 100 and 200 mg BID were comparable
- A non-effective dose of SC-58635 was not identified.

Based on a report completed on: 31 December 1997.